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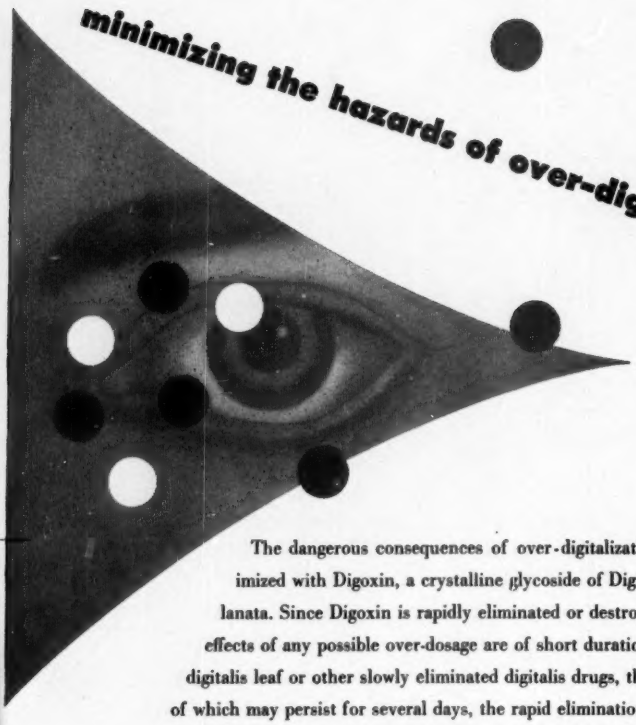

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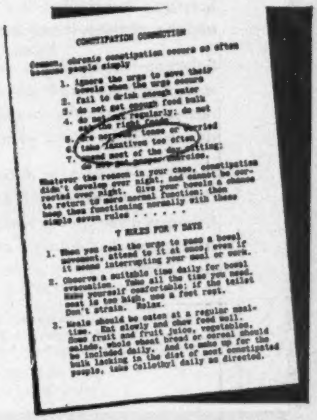

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1. Rev. Gastroenterol. 14:558, 1947.
2. J. Oklahoma M. A. 43:360, 1950.
3. Gastroenterology 13:275, 1949.

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1. Hutcheson, J. M.: Management of Cardiac Failure. *Virginia Med. Monthly*, 74:458, Oct., 1947.
2. Noth, P. H.: Pick's Disease: A Record of Eight Years' Treatment with Salyrgan, Ammonium Nitrate, and Abdominal Paracentesis. *Proc. Staff Meet. Mayo Clin.*, 12:513, Aug. 18, 1937.

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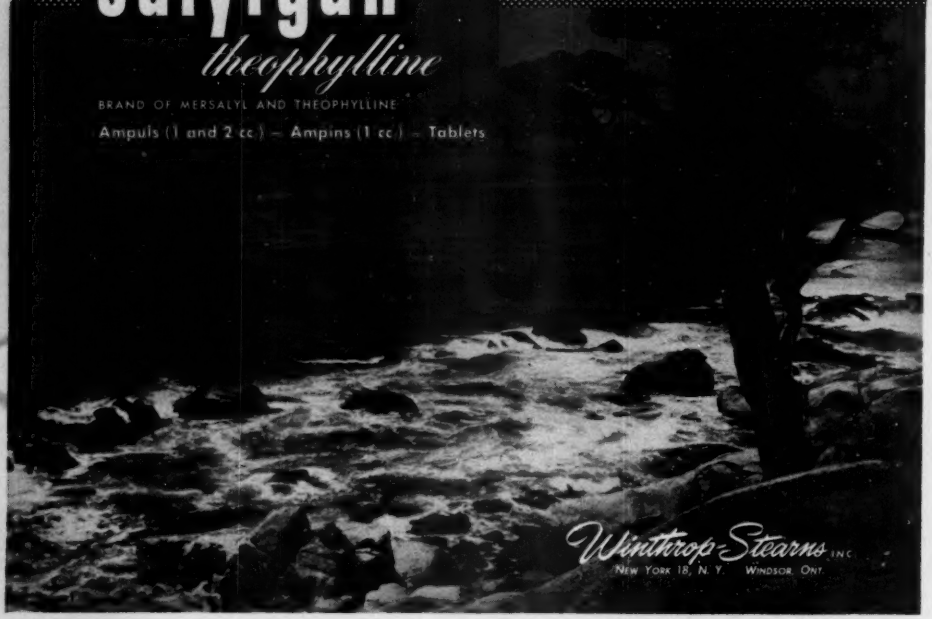

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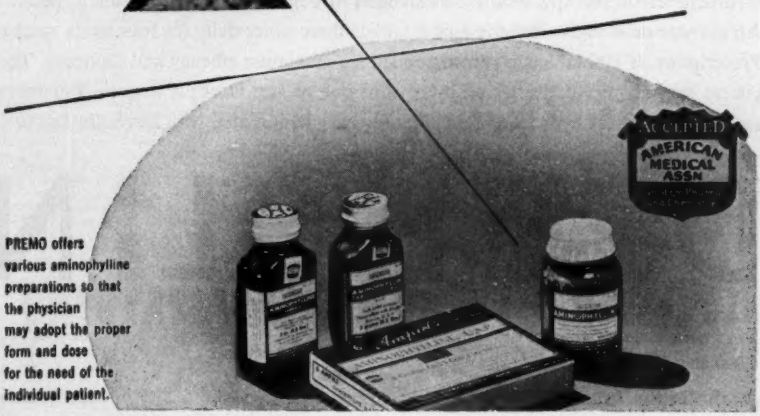

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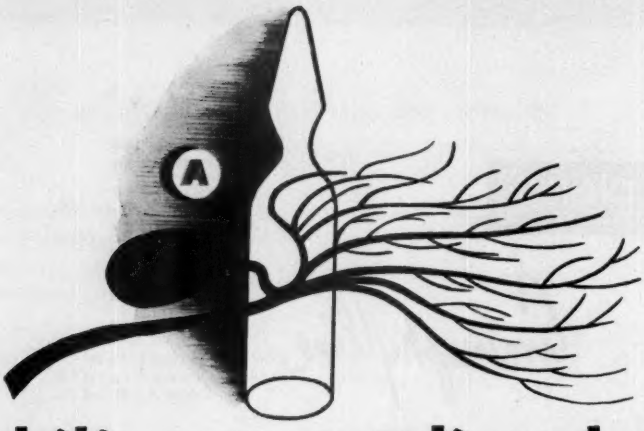

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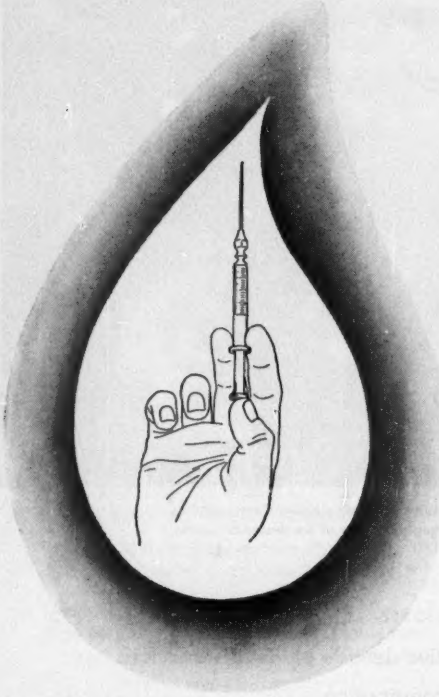

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CONTENTS

PAGE

Titrated, Regularly Spaced Radioactive Phosphorus or Spray Roentgen Therapy of Leukemias. EDWIN E. OSGOOD, M.D., PORTLAND, ORE. 329

Studies on Antibiotic Synergism and Antagonism: The Interference of Chloramphenicol with the Action of Penicillin. E. JAWETZ, M.D., PH.D.; J. B. GUNNISON, M.A.; R. S. SPECK, M.D., AND V. R. COLEMAN, B.A., SAN FRANCISCO 349

Antistreptolysin O Response Following Hemolytic Streptococcus Infection in Early Childhood. LOWELL A. RANTZ, M.D.; MARGARET MARONEY, M.D., AND JOSEPH M. DI CAPRIO, M.D., SAN FRANCISCO 360

Multilobar Pulmonary Venous Obstruction with Pulmonary Hypertension: "Protective" Arterial Lesions in the Involved Lobes. JESSE E. EDWARDS, M.D., AND HOWARD B. BURCHELL, M.D., ROCHESTER, MINN. 372

Intermittent Peritoneal Lavage in Nephrectomized Dogs and Its Application to the Human Being. ARTHUR GROLLMAN, PH.D., M.D.; LOUIS B. TURNER, M.D., AND JAMES A. MCLEAN, M.D., WITH THE TECHNICAL ASSISTANCE OF MAURINE GIESE, WILLIAM M. OTT AND GORDON M. GAFFORD, DALLAS, TEXAS 379

Diffuse Calcification of the Pancreas. BRUNO J. PETERS, M.D.; JOSEPH M. LUBITZ, M.D., AND M. C. F. LINDERT, M.D., WOOD, WIS. 391

CASE REPORTS:

Malignant Tumors of the Duodenum: Report of Two Cases. NATHANIEL H. SCHWARTZ, M.D.; ROY C. SWINGLE, M.D., AND EDWARD A. RAYMOND, M.D., VALHALLA, N. Y. 410

Gaucher's Disease with Megaloblastic Bone Marrow: Response to Therapy. MENDEL KRIM, M.D.; ARTHUR SAWITSKY, M.D.; DAVID KROHN, M.D., AND LEO M. MEYER, M.D., NEW YORK 418

PROGRESS IN INTERNAL MEDICINE:

Syphilis: Review of the Recent Literature (Concluded). HERMAN BEERMAN, M.D.; LESLIE NICHOLAS, M.D.; WILLIAM T. FORD, M.D., AND MINERVA S. BUERK, M.D., PHILADELPHIA, WITH THE COLLABORATION OF FRANK W. REYNOLDS, M.D., AND T. GUTHE, M.D., GENEVA, SWITZERLAND 424

NEWS AND COMMENT 469

BOOK REVIEWS 470

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VOLUME 87 MARCH 1951 NUMBER 3

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TITRATED, REGULARLY SPACED RADIOACTIVE PHOSPHORUS OR SPRAY ROENTGEN THERAPY OF LEUKEMIAS

EDWIN E. OSGOOD, M.D.
PORTLAND, ORE.

THE EVALUATION of a new therapy for chronic leukemias is difficult because of the diverse course of untreated patients, the differing stages of the disease when patients are first seen by a physician, the frequent uncertainty concerning the correct date of onset and the presence of other variables making comparison with published data on other series of patients less satisfactory than the ideally designed experiment. Yet, with a treatment that seems to be giving comfort and years of essentially normal living, the use of alternate or randomly selected, untreated controls in so serious a disease seems unjustified.

It is the purpose of this paper to present the principles of a treatment in use since 1941 in sufficient detail that others may be able to use it and to present enough of the evidence of its merits that others may choose to aid in its final evaluation. This of necessity will involve study of more patients over a longer period than any one group is likely to find possible.

PRINCIPLES OF THE METHOD OF TITRATED, REGULARLY SPACED TOTAL BODY IRRADIATION

Marrow culture studies[1] showed that the effect of small doses of ionizing radiation on either normal or leukemic cells was to decrease the rate of cell division. To accomplish this effect, the rays must reach the cell; no indirect action could be

From the Division of Experimental Medicine, Department of Medicine, University of Oregon Medical School.

Read before the Second Congress of the International Society of Hematology, Aug. 23, 1950, in Cambridge, England.

This work was supported in part by Grants-in-Aid from the Medical Research Foundation of Oregon, the Damon Runyon Cancer Research Fund, Mr. John C. Higgins and the American Cancer Society on recommendation of the Committee on Growth of the National Research Council. The P^{32} used in this investigation was supplied by Clinton Laboratories, Knoxville, Tenn., and obtained on allocation from the Isotopes Division, United States Atomic Energy Commission.

1. Osgood, E. E., and Brownlee, I. E.: Culture of Human Marrow: Details of a Simple Method, J. A. M. A. **108**:1793-1796 (May 22) 1937. Osgood, E. E., and Bracher, G. J.: Culture of Human Marrow: Studies of the Effects of Roentgen-Rays, Ann. Int. Med. **13**:563-575 (Oct.) 1939. Osgood, E. E.: Marrow Cultures, in A Symposium on the Blood and Blood-Forming Organs, Madison, Wis., University of Wisconsin Press, 1939, pp. 219-241; Effects of Irradiation on Leukemic Cells in Marrow Cultures, Proc. Soc. Exper. Biol. & Med. **45**:131-135 (Oct.) 1940. Osgood, E. E.; Aebersold, P. C.; Erf, L. A., and Packham, E. A.: Studies of the Effects of Million Volt Roentgen Rays, 200 Kilovolt Roentgen Rays, Radioactive Phosphorus, and Neutron Rays by the Marrow Culture Technique, Am. J. M. Sc. **204**:372-381 (Sept.) 1942.

expected.[2] Any action on leukemic cells which might be thought to be selective appeared rather to be due to their shorter life span and shorter intermitotic interval as compared with the corresponding normal cell.

It seemed logical, therefore, to accept the fact that one could not hope that radiation would destroy all leukemic cells and so should stop using massive doses and try to find that dose and interval which would cause no discomfort and would still inhibit cell division without destroying the most sensitive leukemic cells. One should "titrate" the radiation to fit the patient in order to achieve the best obtainable state of health and should use all available criteria to aid in selecting a dose to be given at regularly spaced intervals which maintains that state as long as possible. The ideal first dose is the largest dose which has been observed never to constitute overtreatment for the patient with the most radiosensitive cells. The ideal interval between doses until the patient attains an optimum state of health is the shortest interval that permits evaluation of the effects of the preceding dose, modified as the individual situation and response of each patient indicate. The ideal dose and interval after optimum health is attained are the smallest dose and the longest interval that will maintain that state. The method of administering therapy should insure that every leukemic cell is reached at the same time by an equal dose. All available

TABLE 1.—*Procedures at First Visit*

1.	Careful history, physical examination and indicated laboratory studies to establish an accurate and complete diagnosis and an understanding of the patient's immediate physical and psychic needs
2.	Explanation of the disease and the therapy, including the importance of a high protein, high calory, cellulose-free diet in six small feedings daily until the hypermetabolism and "small stomach" syndrome have been corrected; psychotherapy, antibiotics and transfusions as indicated [4]; warning against tooth extractions, elective surgical treatment and pregnancy
3.	Initial dose of roentgen or P^{32} therapy.

methods should be used for the diagnosis and control of associated diseases and complications. Treatment must be individualized to meet the particular needs of each patient at each visit.

Biologic variation of cells and of the total person is so great that only a range of specific details found to be satisfactory can be given. The *sine qua non* of the therapy to be described is the judgment of the clinician, who must thoroughly understand the patient, the disease and the therapeutic methods available.

SPECIFIC DETAILS OF THE THERAPY

The minimal requirements for such a program include a staff consisting of a competent hematologist, a hematological technologist, a radiologist (if x-ray is being utilized) or a biophysicist (if radioactive phosphorus [P^{32}] is being utilized) and facilities for physical examination, laboratory studies, marrow aspirations, a "hot" laboratory for the preparation, storage and administration of the therapeutic P^{32} and an assay laboratory for standardization of the P^{32}, with the usual equipment.[3]

2. Osgood, E. E.: Is the Action of Roentgen Rays Direct or Indirect? An Investigation of This Question by the Method of Human Marrow Culture, Am. J. Roentgenol. **48**:214-219 (Aug.) 1942.

3. Safe Handling of Radioactive Isotopes, Handbook 42, United States Department of Commerce, National Bureau of Standards, 1949.

The procedures at the first visit are outlined in table 1. The essential steps in diagnosis and psychotherapy have been presented elsewhere.[4] The criteria of disease classification and the nomenclature used are those of the Committee for Clarification of the Nomenclature of Cells and Diseases of the Blood and Blood-Forming Organs.[5]

As is true of all therapy, no satisfactory program for the individual patient can be planned until an adequate history has been taken to evaluate the patient's social, economic, geographic and physical status and to become acquainted with the person. All associated diseases are treated. The marked hypermetabolism and protein deficiency observed when patients are first seen often require a month or two on a diet consisting largely of meat, milk, eggs, cheese and bran-free cereals. When the spleen is enlarged, this diet should be divided into six small feedings daily. Cellulose-containing foods and citrus fruit juices should be interdicted until any tendency to gas formation has disappeared. Within a month or two a normal diet may be gradually resumed.

The radiation factors are outlined in table 2. It should be emphasized that when spray roentgen therapy is used it should include the top of the head to the

TABLE 2.—*Essential Irradiation Factors*

Spray Roentgen Therapy
Rapport with competent radiologist; 200 to 400 kv.; no cone, 0.5 mm. Cu + 1 mm. Al or more filtration; half-value layer = > 1.0 mm. Cu; 80 to 100 cm. target skin distance; top of head to tip of toes to be included; 1 port for children; 2 ports for adults separated at level of umbilicus; each port treated identically each time; doses reported in this article as 10 r mean 10 r to each port as measured in air at skin level; prone and supine on alternate visits
Radioactive Phosphorus Therapy
Sterile, accurately standardized solution prepared from Atomic Energy Commission item S-3 given intravenously, prepared and administered by trained staff with adequate facilities[6]; all P^{32} doses reported in this article were calculated from assays made against United States Bureau of Standards radium D—E standards which were checked against periodic United States Bureau of Standards P^{32} solutions

tip of the toes and that an adult dose of 10 r as specified in this paper means 10 r to the entire body, which necessitates 10 r to each of two ports in adults with most of the x-ray equipment in common use.

Especially important if spray roentgen therapy is used is the rapport between radiologist and clinician.[6] The clinician must be certain that the dosage is given exactly as specified. The radiologist must have confidence that the clinician is

4. Osgood, E. E.: Differential Diagnosis and Treatment of the Leukemias, Northwest Med. **47**:181-185 (March); 257-260 (April) 1948.

5. Committee for Clarification of the Nomenclature of Cells and Diseases of the Blood and Blood-Forming Organs: Fourth Report: Recommended Terms and Definitions for the Leukemias and Lymphomas, Am. J. Clin. Path. **20**:571-574 (June) 1950.

6. Drs. Wallace Haworth, G. B. Isenhart and C. T. Jessell, of Portland, Ore., administered all the spray roentgen therapy given under my supervision to the patients reported on in this article, using a General Electric Maximar 220 kv. machine at 200 kv., with 0.5 mm. Cu added filtration, + 1.0 mm. Al equivalent, half-value layer 1.14 mm. Cu, no cone, 94 cm. target skin distance, at 11.3 r per minute, with a fluoroscopic leaded apron of 0.5 mm. lead equivalent as the shield for the upper or lower half of the body. All dosages are as measured at skin surface with a Victoreen ionization meter controlled by a built-in Victoreen constancy meter. All dosages and intervals were decided on by the staff of the Division of Experimental Medicine. Many other radiologists of the northwestern United States have collaborated in the treatment of other patients. However, all the patients treated by other radiologists had had previous local roentgen therapy on a different schedule and so are not included in this report.

basing his recommendation of dosage and interval on a thorough evaluation of each of the factors outlined in table 3, made on an examination immediately preceding each treatment. Both must clearly understand the objectives of the method, as outlined in table 4.

Table 5 will serve only as a rough guide to dosage. Clinical judgment and skill with the method will improve as experience increases.

The points that differentiate this treatment from other methods of using spray roentgen radiation or P^{32} deserve emphasis. The initial dose should not exceed 10 r of roentgen radiation or 20 microcuries of P^{32} per kilogram of body weight

TABLE 3.—*Criteria for Evaluation of Dose and Interval at Each Visit*

Activities, weight, leukocyte count, erythrocyte count, hemoglobin concentration, bleeding tendency, condition of liver, spleen and lymph nodes
Response to previous dose
Direction of change more important than level
Eight day biologic half-life of P^{32} [7]

TABLE 4.—*Objectives of Therapy*

A uniform dose and interval that maintain patient doing usual activities in usual way
Leukocyte count of 10,000 to 20,000 per cu. mm.
Hemoglobin concentration, erythrocytes, thrombocytes within normal range
Body weight and lymph nodes normal to 1+
No abnormal bleeding, skin lesions or bone pain
Liver and spleen at or above costal margin

TABLE 5.—*Dosage Guide for Treatment of Leukemias*

	Roentgen Therapy		P^{32} Therapy	
Dose and Interval	Lymphocytic	Granulocytic	Lymphocytic	Granulocytic
Maximum 1st dose	10 r	20 r	20 μc./Kg.	40 μc./Kg.
Maximum subsequent dose	25 r		100 μc./Kg.	
Initial intervals	1 to 2 wk.		1 to 3 wk.	
Usual total dose for control	100 r (20 to 240)	150 r (40 to 340)	60 μc./Kg. (40 to 300)	100 μc./Kg. (60 to 400)
Usual time for control	6 wk. (4 to 12)		6 wk. (4 to 12)	
Usual dose for maintenance	10 r/mo. (3 to 25)		6 μc./Kg./mo. (1 to 15)	
Usual interval	6 wk. (2 to 12)		10 wk. (4 to 12)	

in lymphocytic leukemias or twice these values in granulocytic leukemias, since certain patients are so radiosensitive that even a single dose of larger size may constitute overtreatment. The second dose should not be given earlier than one week after the first dose, because a shorter time period does not permit adequate evaluation of the effects of the initial dose. In most instances, the initial dose will be too small and the leukocyte count may increase or the patient's condition deteriorate slightly, but it is far safer to undertreat than to overtreat. No dose should be more than double the preceding dose. The interval should not be increased by more than one week at a time if it is less than four weeks or by over two weeks if it is over four weeks.

Utilize all available criteria in evaluating dosage. This permits treatment of subleukemic and aleukemic as well as leukemic patients, although admittedly the

leukocyte count is the most helpful, single guide. The direction of change in the spleen, liver, lymph nodes, bleeding tendency, leukocyte count and hemoglobin concentration or in the capacity for work and recreational activity is far more important than is the actual level of each. For example, a leukocyte count of 20,000 per cubic millimeter in a person who at the previous visit had a count of 30,000 indicates an increase in interval with a smaller repeat dose or none at all on this visit. A leukocyte count of 20,000 in a patient who had a 10,000 count the last time indicates an increase in dose over the preceding dose, and a leukocyte count of 20,000 in a patient who is oscillating between 15,000 and 20,000 on the same dose and interval indicates a repetition of the dose and interval.

A change in dose is not a substitute for a change in interval. In general, the more acute the leukemia is the shorter the interval needs to be and the more chronic the leukemia is the longer the interval may be. Since patients with chronic leukemia have a life span after onset varying from one to over 20 years, there is a considerable range of interval between one person and another. The 3 year old boy with chronic granulocytic leukemia was the only patient who required intervals of less than two weeks with spray roentgen therapy for maintenance. No patient receiving P^{32} required intervals of less than four weeks for maintenance. The ideal interval for each patient has to be determined by trial; in other words, by titration. After the first two or three doses the interval should be gradually prolonged by one to two weeks at a time.

Since P^{32} has a biologic half-life of eight days,[7] dosage effects are cumulative if the interval is much less than six weeks. One can approximate the retained dose in terms of equivalent P^{32} level by adding one-half the previous dose at one week, one-fourth the previous dose at two weeks, one-eighth the previous dose at three weeks and so on. A somewhat more accurate estimate of the plasma P^{32} level can be obtained by the following procedure: Using semilogarithmic graph paper, locate a point on the zero time intercept, expressed in microcuries per millimeter, at 16 per cent of the preceding dose of P^{32} in microcuries per gram of body weight and another point at eight days corresponding to 50 per cent of the zero intercept value. A line drawn through these two points will give a reasonable estimate of the plasma P^{32} level for any time over 24 hours after the P^{32} was administered. The residual effects of previous doses, similarly plotted, can be added if desired. The erythrocyte P^{32} level will be approximately six times this plasma level at any time after 24 hours and the leukocyte P^{32} level approximately 30 times this plasma level at any time after one week.[7]

7. (*a*) Tivey, H., and Osgood, E. E.: The Biological Half-Life of Radioactive Phosphorus in the Blood of Patients with Leukemia: I. Whole Blood—with Deviations of Observations from Predicted Values and an Estimate of Total-Phosphorus Turnover Rate, Cancer **3**:992-1002 (Nov.) 1950. (*b*) Osgood, E. E., and Tivey, H.: The Biological Half-Life of Radioactive Phosphorus in the Blood of Patients with Leukemia: II. Plasma—with Deviations of Observations from Predicted Values and an Estimate of Total-Phosphorus Turnover Rate, ibid. **3**:1003-1009 (Nov.) 1950. (*c*) Tivey, H., and Osgood, E. E.: The Biological Half-Life of Radioactive Phosphorus in the Blood of Patients with Leukemia: III. Erythrocytes—with Deviations of Observations from Predicted Values, ibid. **3**:1010-1013 (Nov.) 1950. (*d*) Osgood, E. E., and Tivey, H.: The Biological Half-Life of Radioactive Phosphorus in the Blood of Patients with Leukemia: IV. Leukocytes—Radioactive Phosphorus Content and the Relation of Plasma-P^{32} Levels, ibid. **3**:1014-1017 (Nov.) 1950.

The biologic variation in radiosensitivity of the cells of the lymphocytic and granulocytic series in different persons is so great, however, that the clinical response is by far the most important factor in gaging dosage.

Patients who have had previous, intermittent, massive dose roentgen therapy to the spleen or long bones will usually require larger doses than will previously untreated patients, because the more radiosensitive cells have already been eliminated. While of less importance than radiosensitivity as a criterion of dose and interval, body weight should always be taken into consideration in P^{32} therapy. A dose of 1 millicurie to a 100 pound (45.4 Kg.) woman is twice as much as a dose of 1 millicurie to a 200 pound (90.7 Kg.) man.

Note that the most typical doses shown in table 5 are nearer the lower than the upper limits of the range of dosage. Only a few patients require doses above

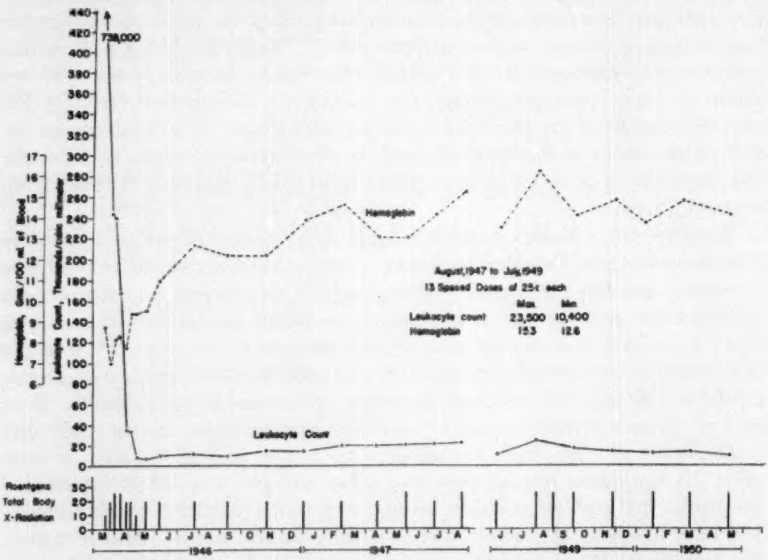

Fig. 1.—Case CLL 4 (6) is a typical example of the method of and response to titrated, regularly spaced total body irradiation. This 59 year old telegraph operator was totally incapacitated at the time treatment was started, March 18, 1946, with anemia, splenomegaly to 10 cm. below the umbilicus and across the midline and loss of weight to 149 pounds (67.6 Kg.). He has worked uninterruptedly since April 10, 1946 and has had no leukocyte count greater than 30,000 per cubic millimeter since April 25, 1946; his weight reached 167 pounds (75.7 Kg.) by Sept. 12, 1946; his spleen had receded to the costal margin by Nov. 7, 1946 and has never subsequently enlarged. Note that the hemoglobin concentration returned to normal without transfusions and that in the total 95 months of his leukemic life, 49 of these after therapy was started, he has never had to be hospitalized. The majority of patients receiving either roentgen or P^{32} therapy respond in this manner. Titration for a few patients with either type of leukemia treated with either type of total body irradiation has been more difficult, as illustrated in figure 2. Compare also with figure 3.

50 microcuries per kilogram, and 100 microcuries per kilogram is usually needed only in the terminal, resistant phase of leukemia. The dosage for control as recorded in table 5 is the total dose, not the individual dose given each week or two. As

shown, the usual maintenance doses are much smaller than the doses for control and the usual interval for maintenance is much longer than the intervals during the control period. For roentgen therapy the usual interval is nearer the lower limits and for P^{32} therapy it is nearer the upper limits of the interval range. While the leukemia could undoubtedly be controlled in some patients given P^{32} therapy if treated at longer intervals, experience indicates that any patient with leukemia ideally should be seen at least every 12 weeks. In special circumstances, such as a planned vacation or business trip, concessions may be made, especially for the patients with the more chronic disease who require only 0.5 millicurie of P^{32} or 10 r of spray roentgen radiation every 12 weeks.

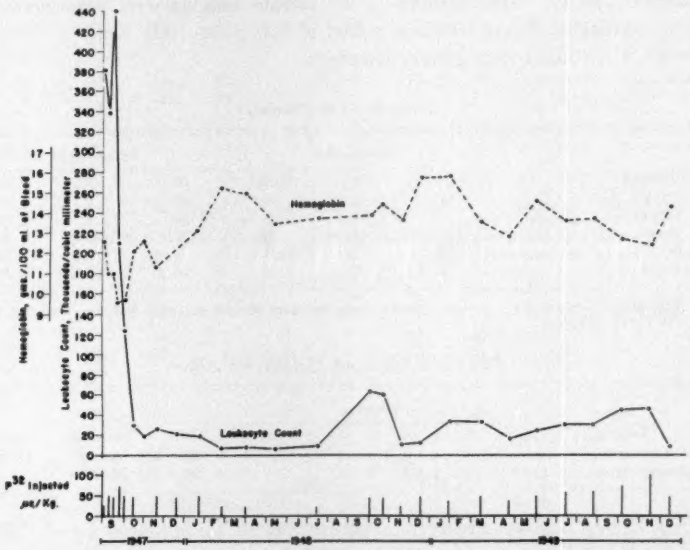

Fig. 2—Case CLG 9 (13) is an example of the adjustments in dose and interval (titration) necessary in the cases more difficult to keep under good control. This 40 year old housewife had noted pallor, weakness and progressive enlargement of the abdomen since Jan. 15, 1947. She had been in the hospital and had received three 500 ml. blood transfusions under the care of her local physician during the month immediately preceding her first treatment on Sept. 2, 1947, at which time her spleen extended 14 cm. below the costal margin and to the right of the midline. The spleen was 1 cm. above the costal margin by Jan. 22, 1948. She had resumed her usual activities by Oct. 30, 1947. She did not again require transfusions or hospitalization until March 30, 1950. She died April 6, 1950 of hematemesis and cerebral hemorrhage. Note that the omission of P^{32} on May 13, 1948 was an error in judgment, as was the too rapid prolongation of the interval after the July 1948 visit. The increasing doses required in the fall of 1949 marked the beginning of an acute leukemic blood picture which was controlled until Feb. 9, 1950 and then was uncontrollable even by higher doses and shorter intervals. In retrospect, changes in dose and interval were made too abruptly in this patient; yet she presented the clinical picture of exuberant health from Oct. 30, 1947 to Feb. 9, 1950. This figure (from Tivey and Osgood [7a]) is reproduced by permission of the copyright owners, Paul B. Hoeber, Inc., Medical Book Department of Harper & Bros., publishers of *Cancer*.

The most important criterion of adequate maintenance dosage is whether or not the patient can carry on his usual activities in his usual way. This means

working full time at his usual employment, indulging in all his usual recreations and leading a normal life in every way.

Once the correct dose and interval for a particular patient are determined, the same dose and interval should be maintained, with only minor variations, over many years (fig. 1), although for occasional patients titration is more difficult, as illustrated in figure 2.

EVIDENCE OF THE VALUE OF THE TREATMENT

The data on sex and social status of the patients treated are summarized in table 6 and the data on age distribution in table 7. All patients were white and native born. The indigent patients were all residents of Portland, Ore., or the immediate vicinity. The majority of the private patients were residents of the Pacific Northwest, living within a radius of 500 miles (805 Km.) of Portland, although a few came from greater distances.

TABLE 6.—*The Patients**

	Granulocytic			Lymphocytic		
Status	M	F	Total	M	F	Total
Private	5	13	18	20	9	29
Indigent	1	1	2	5	4	9
Total	6	14	20	25	13	38
Dead	5	7	12	10	4	14
Living	1	7	8	15	9	24

* This group includes every patient referred since 1941 with chronic leukemic leukemia who had had no previous specific therapy.

TABLE 7.—*Age (Last Birthday) at Onset*

	Decades											
Leukemia	1	2	3	4	5	6	7	8	9	No.	Range, Yr.	Mean Age
Granulocytic	1	1	4	5	1	3	3	2	0	20	(8 to 71)	42
Lymphocytic	0	0	1	2	6	10	13	5	1	38	(27 to 81)	58

The clinical courses of two typical patients are shown in figures 1 and 2. Figure 3 is included for comparison. The essential data on each of the 20 patients with chronic leukemic granulocytic leukemia are shown in figure 4 and table 8 and on the 38 patients with chronic leukemic lymphocytic leukemia in figures 5 and 6 and tables 9 and 10. The cases in tables 8, 9 and 10 are arranged in the sequence of the dates of starting therapy and in figures 4, 5 and 6 in the sequence of the dates of onset of leukemia, which should be truly random order. The key to figures 4, 5 and 6 should be self explanatory.

This preliminary report includes every private patient with chronic leukemic granulocytic (CLG)[8] or chronic leukemic lymphocytic (CLL)[8] leukemia with a leukocyte count over 15,000 per cubic millimeter referred for treatment and every such indigent patient seen in the University of Oregon Medical School Hospitals

8. Clinical data for patients whose case number is prefixed with CLG will be found in table 8 and figure 4 and for those whose number is prefixed with CLL in tables 9 or 10 and in figures 5 or 6. The initial case number designates the sequence of start of treatment. The parenthetical number designates the sequence of onset of leukemia.

and Clinics since 1941 who had not previously had roentgen, nitrogen mustard or urethan therapy. One patient, case CLL 34 (30), had potassium arsenite solution (Fowler's solution) for one month only before P^{32} therapy was started. No other patient received this solution, urethan or nitrogen mustard at any time.

TABLE 8.—*Total Duration, Duration Since Therapy, Time at Usual Activity, Time with Leukocyte Counts Under 30,000 (All in Months) and Complications and Associated Diseases in Cases of Chronic Leukemic Granulocytic Leukemia Arranged in the Sequence in Which Therapy Was Begun*

Date of 1st Treatment	Sequence of Start of Treatment	Sequence of Onset	Total Duration	Duration Since Treatment	Time at Usual Activity		Time Since Treatment to Reduce Leukocyte Count to < 30,000	Total Time Leukocyte Count < 30,000	Comment, Complications and Associated Diseases
					Since Treatment	Total			
5/13/42	1	(4)	52	40	31	41	4.5	18	Case 1, fig. 1 [4]; 3 yr. old boy: measles, otitis media, tonsillectomy and adenoidectomy, sinusitis, bilateral antrotomy
6/11/43	2	(7)	28	28	17	19	1.5	15	Appendicitis, appendectomy
1/10/44	3	(6)	55	43	?	?	1.0	?	Left region; omitted from post-treatment tabulations
3/ 2/44	4	(9)	22	13	3	8	1.4	7	Psychoneurosis, fractured leg
4/13/44	5	(8)	14	2	0	0	...	0	In extremis from leukemia when first seen
4/26/44	6	(2)	125	55	?	?	1.5	?	Left region; omitted from post-treatment tabulations
12/ 1/44	7	(10)	21	5	0	0	0	5	Amebic dysentery, fatal transfusion reaction
		Cases 1 to 7 Treated with Spray Roentgen Therapy; All Others with P^{32} Only							
6/19/47	8	(3)	130 *	35	34	137	0	35	Pneumonia of lower lobe of left lung
9/ 2/47	9	(13)	30	31	28	35	1.5	28	None; course of case shown in fig. 2
10/ 3/47	10	(11)	34	16	11	22	2.0	11	Atherosclerosis, bronchopneumonia, pyelitis, congestive heart failure, terminal cerebral vascular accident
12/30/47	11	(12)	44 *	29	28	37	0.75	28	Hypothyroidism, obesity
3/ 9/48	12	(15)	16	7	3	9	1.0	6	Diabetes mellitus, tuberculous adenitis, terminal miliary tuberculosis
4/ 5/48	13	(14)	27	15	12	23	2.0	12	Hypertensive cardiovascular disease, terminal pulmonary edema
4/13/48	14	(17)	16	14	13	13	2.0	12	Delivered normal full term infant; chickenpox, terminal acute glomerulonephritis
5/25/48	15	(5)	107 *	24	24	107	1.0	22	None
5/28/48	16	(1)	143 *	24	17	136	1.0	23	Atherosclerosis, hypertension, pyelonephritis
6/22/48	17	(18)	25 *	23	23	25	2.5	15	None
1/17/49	18	(19)	18 *	17	14	14	1.0	15	Referred with temperature of 105.5 F., abdominal wall abscess; leukemia discovered after uterine suspension and tube ligation
7/ 5/49	19	(20)	13 *	11	11	13	1.0	11	None
7/20/49	20	(16)	29 *	11	10	27	1.75	6	Premature infant delivered; tube ligation, third degree retroversion, pyoderma
Mean 20 cases			48.3	21.9	..	..	...	..	
Mean 18 cases			..	..	15.5	37.0	...	14.9	
Mean 17 cases			..	..	..	..	1.63	..	
% total duration			..	45.3	..	84.6	...	..	
% of duration since treatment			..	..	82.0	..	...	79.1	

* Alive as of last visit prior to July 1, 1950.

The exact date of death is known for every patient who died, and the exact status is known for every patient in this series who is living. One patient, case CLG 3 (6), moved to Iowa, and another, case CLG 6 (2), moved to Pennsylvania. These two patients, after starting the described therapy, were later treated by others. They were omitted in calculating the mean duration of time at usual activity and time with leukocyte count under 30,000 (table 8) because personal, firsthand

information was lacking, although each was under good control, doing her usual housework when she left this region.

No patient during this time was refused therapy because he was too ill. One patient was excluded from this series who was never actually seen, having died

TABLE 9.—*Total Duration, Duration Since Therapy, Time at Usual Activity, Time with Leukocyte Counts Under 30,000 (All in Months) and Complications and Associated Diseases in Twenty Cases of Chronic Leukemic Lymphocytic Leukemia Arranged in the Sequence in Which Therapy Was Begun*

Date of 1st Treatment	Sequence of Start of Treatment	Sequence of Onset	Total Duration	Duration Since Treatment	Time at Usual Activity: Since Treatment	Time at Usual Activity: Total	Time Since Treatment to Reduce Leukocyte Count to < 30,000	Total Time Leukocyte Count < 30,000	Comment, Complications and Associated Diseases
2/ 7/44	1	(5)	25	5	0	0	0	5	Hypertensive cardiovascular disease, boat accident, terminal cerebral vascular accident
12/ 4/44	2	(8)	15	10	0	0	3.5	6.0	Thrombocytopenic bleeding before treatment, acquired hemolytic anemia
8/ 6/45	3	(3)	114	34	30	110	2.25	29	Chronic bronchitis, bronchiectasis, pyelitis; P^{32} last 5 mo. of life
3/18/46	4	(6)	95 *	50	49	90	1.5	48	None; course of case shown in fig. 1; case 2, fig. 2 [4]
7/24/46	5	(1)	167	22	21	166	8.25	16	None; case 4 [4]; P^{32} last 3 wk. of life
11/22/46	6	(9)	71 *	42	42	71	0.5	41	None
		Cases 1 to 6 Treated with Spray Roentgen Therapy; All Others with P^{32} Only							
3/15/47	7	(2)	143 *	38	36	140	2.5	36	Hypertensive cardiovascular disease, paroxysmal auricular tachycardia, obesity
4/19/47	8	(13)	48 *	37	36	40	1.0	36	None
5/22/47	9	(17)	40 *	37	37	40	0	37	None
9/ 8/47	10	(12)	44 *	32	30	36	1.25	31	Herniorrhaphy, varicose veins, hemorrhoids, corneal ulcers
2/27/48	11	(21)	33 *	26	21	27	3.5	23	Hypothyroidism, prostatic hyperplasia, Bell's palsy
4/27/48	12	(16)	17	3.0	0	9	1.0	2	Carcinoma of the pancreas, terminal postoperative peritonitis after Whipple operation
5/12/48	13	(18)	28 *	25	25	36	0	25	None
6/ 3/48	14	(4)	119 *	24	22	112	0.5	23	None
6/11/48	15	(24)	25 *	24	23	23	1.25	23	Chronic bronchitis and bronchiectasis
6/23/48	16	(25)	25 *	24	23	24	0.5	23	Atherosclerosis
7/15/48	17	(19)	38	21	17	25	0.75	20	Diabetes mellitus, carcinoma of the prostate, terminal myocardial infarction
7/30/48	18	(23)	26 *	23	23	26	0.5	22	Hypertensive cardiovascular disease, paroxysmal auricular tachycardia, obesity
9/28/48	19	(27)	6	4	0	0	0	4	Old and recurrent terminal thrombosis of right middle cerebral artery
12/28/48	20	(20)	22 *	16	16	21	0	16	None
Mean 20 cases			55.0	24.6	22.6	49.8	...	23.0	
Mean 15 cases			..	..	..	..	1.58	..	
% total duration			..	44.6	..	90.5	...	..	
% duration since treatment			..	..	91.8	..	...	94.9	

* Alive as of last visit prior to July 1, 1950.

en route to the first appointment. A patient who died four hours after the first dose of P^{32} and one who died two days after the first dose of P^{32} of unrelated diseases, cases CLL 21 (32) and 32 (20), are included, as are patients who were almost moribund from their leukemia when first seen—cases CLG 5 (8) and CLL 2 (8), 27 (11) and 28 (29). Others were referred early in the course of their disease before symptoms had developed—cases CLG 17 (18) and 19 (20) and CLL 9 (17) and 13 (18).

The patients with subleukemic and aleukemic leukemia were excluded from this preliminary report. They have, however, been treated by essentially the same method, although the leukocyte count could not be used as a criterion for dosage. Some of the most striking improvements occurred in this group. They will be reported at another time.

TABLE 10.—*Total Duration, Duration Since Therapy, Time at Usual Activity, Time with Leukocyte Counts Under 30,000 (All in Months) and Complications and Associated Diseases in Eighteen Additional Cases of Chronic Leukemic Lymphocytic Leukemia Arranged in the Sequence in Which Therapy Was Begun*

Date of 1st Treatment	Sequence of Start of Treatment	Sequence of Onset	Total Duration	Duration Since Treatment	Time at Usual Activity		Time Since Treatment to Reduce Leukocyte Count to < 30,000	Total Time Leukocyte Count < 30,000	Comment, Complications and Associated Diseases
					Since Treatment	Total			
1/14/49	21	(32)	0	0	0	0	...	0	Diabetes mellitus, hypertensive cardiovascular disease, terminal congestive heart failure; died 4 hr. after first dose of P^{32}
3/14/49	22	(33)	2	1	0	0	...	0	Adenocarcinoma of appendix with peritoneal implantations, pyelonephritis
3/25/49	23	(7)	72 *	15	15	72	1.5	14	Peptic ulcer, bronchitis, bronchiectasis
4/ 8/49	24	(14)	44 *	14	14	42	2.0	12	Allergic sinusitis, rhinitis
5/13/49	25	(28)	21 *	12	12	21	0	12	Dysphagia, recurrent laryngeal nerve paralysis from pressure by lymph nodes
6/ 1/49	26	(22)	30 *	12	0	15	0.75	11	Acute glaucoma, hypertensive cardiovascular disease, bronchitis, acquired hemolytic anemia
7/ 2/49	27	(11)	38	1	0	0	0	1	Congestive heart failure, acquired hemolytic anemia, gastroenteritis, terminal pulmonary infarction
7/ 6/49	28	(29)	12	1	0	8	0.5	1	Migrating thrombophlebitis, acquired hemolytic anemia
8/ 8/49	29	(10)	52 *	10	0	0	0	10	Bedfast from rheumatoid arthritis
8/17/49	30	(31)	19 *	10	6	6	0	10	Hypertensive cardiovascular disease
9/21/49	31	(34)	15 *	9	5	10	1.25	8	Urethral prolapse, cystitis
9/23/49	32	(20)	27	0	0	26	...	0	Peptic ulcer, hematemesis, terminal thrombosis of right middle cerebral artery; died 2 days after first dose of P^{32}
9/23/49	33	(36)	8	4	0	0	0	4	Atherosclerosis, congestive and anginal heart failure, terminal myocardial infaret, mesenteric thrombosis
10/ 4/49	34	(30)	21 *	9	8	19	3	5	Duodenal peptic ulcer; potassium arsenite solution for 1 mo. before treatment
10/13/49	35	(35)	7	2	0	0	...	0	81 years old; peritonsilar abscess, bronchiectasis, atherosclerosis, auricular fibrillation, terminal pulmonary hemorrhage
10/14/49	36	(37)	10 *	8	0	0	1	7	Myocardial infarction, atherosclerotic heart disease
10/17/49	37	(38)	9 *	8	6	6	3	5	Leukemia discovered at appendectomy for ruptured appendix
11/ 9/49	38	(15)	42 *	6	0	36	1	4	Acquired hemolytic anemia, splenectomy
Mean 38 cases			40.3	16.3	13.6	33.1	...	15.0	
Mean 24 cases			..	..	..	..	1.57	..	
% total duration			..	40.5	..	82.2	...	..	
% duration since treatment			..	..	83.5	..	...	91.9	

* Alive as of last visit prior to July 1, 1950.

The previously treated patients were excluded from this report, even though they included all the patients with lymphocytic leukemia started on therapy prior to 1944 and several patients still alive with life spans of over 12 years since the onset of the disease. Including these patients increased the average duration so much that it was apparent some factor other than the therapy was responsible. This factor is undoubtedly a nonrandom sampling with selection for a long course. It is

obvious that if several patients with the same date of onset are given one therapy only those who survive to the time of referral for a new therapy could be referred and these would be the ones with the more chronic disease. For this reason, the data of the reports summarized in tables 12 and 13 are given both as the authors recorded them and as recalculated for only those patients not previously treated by other methods, when this was possible.

At the first visit the date of onset was determined as accurately as possible. Since chronic leukemia may have an insidious onset, it was often impossible to ascertain an exact date. When the symptoms developed during one month, say August 1944, the date was recorded as Aug. 15, 1944; if during the "fall of 1944," the date was recorded as Nov. 15, 1944; if during the "year 1939," the date was recorded as June 30, 1939. Ages were recorded as of this date of onset, calculated

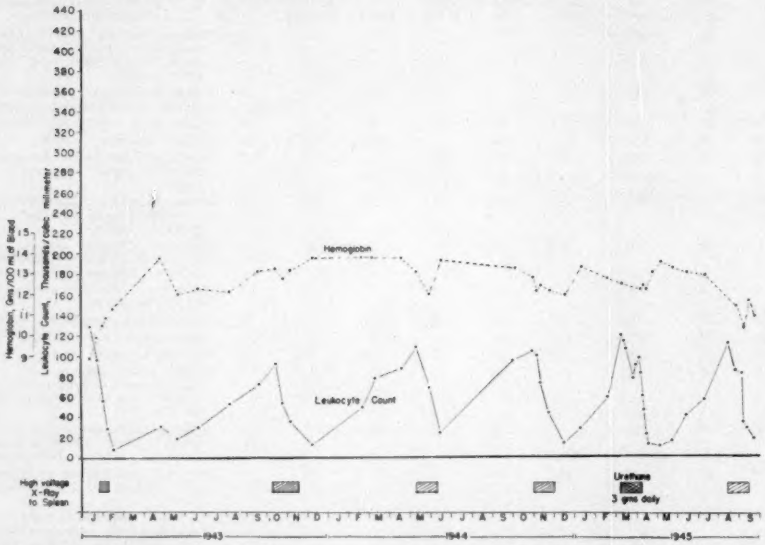

Fig. 3.—For comparison with figures 1 and 2; this is the typical course of a case of chronic leukemic granulocytic leukemia treated by recognized authorities with the methods now in most general use. Data on case 19 given in figure 5 of Paterson and others (*Lancet* **1**:680[May 11] 1946) have been replotted to the same scale as figures 1 and 2 of the present report. Note the sequence of remission and relapse and the large percentage of the total time that the leukocyte count was greater than 30,000 per cubic millimeter.

from the age at the last birthday, as given at the first visit. Often objective evidence was available; for example, the onset of disease in case CLL 5 (1), with a survival of 14 years, was dated from a photograph taken in 1934, showing the patient's collar tied together with a cord because of the great enlargement of the lymph nodes in his neck. Some patients, cases CLG 18 (19) and CLL 22 (33) and 36 (37), were so ill from other diseases that the time of onset of symptoms due to leukemia could not be determined; the onset was then recorded as the date the patient was first seen.

Because all were referred patients, the diagnosis of leukemia had usually been made or suspected by one or more other physicians. Marrow studies confirmed

the diagnosis for all patients with leukocyte counts under 50,000 per cubic millimeter, and the diagnosis of leukemia was substantiated for every patient in this group who was studied at necropsy.

A few patients were observed for a period of months to rule out infectious lymphocytosis before therapy was started, but in the majority therapy was started the same day they were first seen. This is contrary to the practice of many physicians in treating chronic leukemias, and prior to 1941 it was my practice also to withhold therapy until symptoms developed. However, the patients who had mild symptoms felt so much better soon after the start of therapy that it was decided to begin immediate therapy for all patients, including those who claimed to feel perfectly well. Subsequently, these patients also reported an improvement in their feeling of well-being. It is only logical that this should occur, since the hyper-

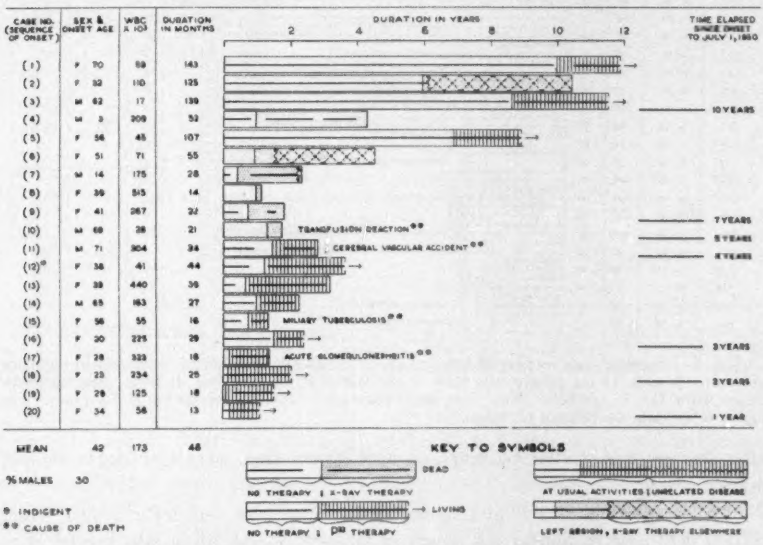

Fig. 4.—Essential data on 20 cases of chronic leukemic granulocytic leukemia arranged in sequence of onset of the disease, showing graphically type of treatment, duration of life, time at usual activities (center line), disability due to concurrent disease (wavy line), disability due to leukemia (no center line) and cause of death when not leukemia. The scale at right indicates the number of years to July 1, 1950 these patients could have lived. The arrows indicate patients alive at last visit prior to July 1, 1950. See tables 8, 9 and 10 for causes of disability indicated by wavy line.

metabolism and increased protein turnover are reduced. The benefit is similar to that which a patient with hyperthyroidism receives when the hypermetabolism is corrected. We do not withhold insulin until the diabetic patient becomes incapacitated; why should we withhold effective therapy for patients with chronic leukemia until they are incapacitated? We do not treat the patient in diabetic coma until he is rehabilitated and then omit insulin until he is again incapacitated. If we did, we might speak of producing "remissions" of a certain length in diabetes mellitus. It seems probable that the sequence of remission and relapse (fig. 3) is an artefact of our previous methods of treating patients having chronic leukemia and that the

same sequence would be observed in persons with diabetes mellitus or pernicious anemia if we waited until symptoms recurred before we gave the next course of therapy.

The proportion of the total leukemic life spans spent at the patients' usual activities (tables 8, 9 and 10) is greater than I have observed personally or seen reported with any other method of treatment. Of the total 208 years of leukemic life represented by this series, 167 [9] were spent in essentially normal living for persons of like age and sex, and much of the nonworking time was due to concurrent disease entirely unrelated to leukemia. More important, of 80 leukemic years

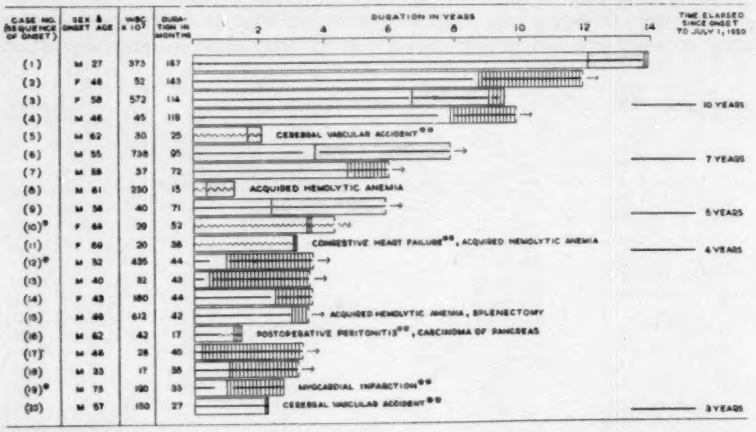

Fig. 5.—Essential data on first 20 cases of chronic leukemic lymphocytic leukemia in sequence of onset. In case 14 the patient was alive at the last visit prior to July 1, 1950. See legend to figure 4 for key to symbols. Note that mean duration of life for this group is 5.2 years. See figure 6 for data on balance of series.

after therapy was started, 66 years, or over 80 per cent, were spent in essentially normal living.

The proportion of the total post-therapy time with leukocyte counts under 30,000 per cubic millimeter, as shown in tables 8, 9 and 10, is also greater than that usually observed.

Results of Therapy.—The mean durations of life and the fraction surviving at each interval are shown in table 11 and are compared in tables 12 and 13 with results from a few representative published reports [10] of other methods of treatment.

9. The known time at usual activity for cases CLG 3 (6) and CLG 6 (2) are included in this value.

10. (*a*) Minot, G. R.; Buckman, T. E., and Isaacs, R.: Chronic Myelogenous Leukemia: Age Incidence, Duration, and Benefit Derived from Irradiation, J. A. M. A. **82**:1489-1494 (May 10) 1924. (*b*) Hoffman, W. J., and Craver, L. F.: Chronic Myelogenous Leukemia: Value of Irradiation and Its Effect on the Duration of Life, ibid. **97**:836-840 (Sept. 19) 1931. (*c*) Wintrobe, M. M., and Hasenbush, L. L.: Chronic Leukemia: The Early Phase of Chronic Leukemia, the Results of Treatment and the Effects of Complicating Infections; a Study of 86 Adults, Arch. Int. Med. **64**:701-718 (Oct.) 1939. (*d*) Pascucci, L. M.: Chronic Leukemia: A Statistical Study of Symptoms, Duration of Life, and Prognosis, Radiology **39**:75-80 (July)

The fraction surviving is given for all patients as if observed at the designated time after onset in the upper block in table 11 [11] and as of the last visit prior to July 1, 1950 for the total series and for the groups surviving three to 14 and five to 14 years.

A few excellent articles on the treatment of leukemia have appeared which deserve summary but did not include data in a form which would permit inclusion in tables 12 and 13.

Paterson and her co-workers [12] reported on 34 persons having chronic leukemic granulocytic leukemia and four having the acute disease treated with urethan. Of the 34 patients who had chronic leukemia 22 received roentgen therapy either before

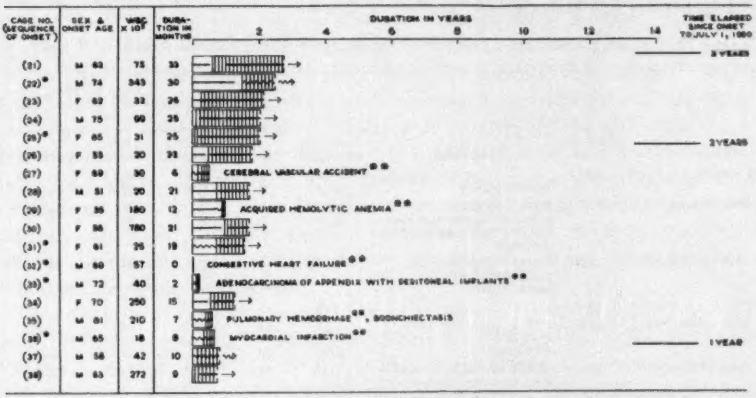

Fig. 6.—Essential data on last 18 cases of chronic leukemic lymphocytic leukemia in sequence of onset. See legend to figure 4 for key to symbols. The mean age at onset for the series of 38 patients was 58 years. The mean leukocyte count was 155,000. The mean duration in months was 40. Men were 66 per cent of the series.

1942. (*e*) Reinhard, E. H.; Moore, C. V.; Bierbaum, O. S., and Moore, S.: Radioactive Phosphorus as a Therapeutic Agent: A Review of the Literature and Analysis of the Results of Treatment of 155 Patients with Various Blood Dyscrasias, Lymphomas, and Other Malignant Neoplastic Diseases, J. Lab. & Clin. Med. **31**:107-218 (Feb.) 1946. (*f*) Wintrobe, M. M., and Huguley, C. M., Jr.: Nitrogen-Mustard Therapy for Hodgkin's Disease, Lymphosarcoma, the Leukemias, and Other Disorders, Cancer **1**:357-382 (Sept.) 1948. (*g*) Lawrence, J. H.; Dobson, R. L.; Low-Beer, B. V. A., and Brown, B. R.: Chronic Myelogenous Leukemia: A Study of 129 Cases in Which Treatment Was with Radioactive Phosphorus, J. A. M. A. **136**:672-677 (March 6) 1948. (*h*) Minot, G. R., and Isaacs, R.: Lymphatic Leukemia: Age Incidence, Duration, and Benefit Derived from Irradiation, Boston M. & S. J. **191**:1-9 (July 3) 1924. (*i*) Bethell, F. H.: Lymphogenous (Lymphatic) Leukemia: Diagnostic, Prognostic and Therapeutic Considerations Based on an Analysis of Its Morphologic and Clinical Variants, J. A. M. A. **118**:95-99 (Jan. 10) 1942. (*j*) Lawrence, J. H.; Low-Beer, B. V. A., and Carpender, J. W. J.: Chronic Lymphatic Leukemia: A Study of 100 Patients Treated with Radioactive Phosphorus, ibid. **140**:585-588 (June 18) 1949.

11. It is interesting to note that these percentage survival figures for the combined series of granulocytic and lymphocytic leukemias fit a semilogarithmic straight line distribution. Projection of this line suggests that 50 per cent of this group of patients will be alive six years after the onset of their leukemia.

12. Paterson, E.; Ap Thomas, I.; Haddow, A., and Watkinson, J. M.: A Further Report on the Action of Urethane in Leukemia, in Approaches to Tumor Chemotherapy, Washington, D. C., American Association for the Advancement of Science, 1947, pp. 401-415.

TABLE 11.—*Chronic Leukemic Granulocytic and Lymphocytic Leukemias Treated by Titrated, Regularly Spaced Total Body Irradiation: Fraction Surviving and Mean Life Span*

Time Since Onset, Yr.	Granulocytic	Lymphocytic	Total Series	Per Cent
0.5	20/20	35/38	55/58	95
1	20/20	30/36	50/56	89
2	13/18	23/25	37/43	86
3	8/16	15/20	24/36	67
4	6/11	8/11	14/22	64
5	4/10	7/9	11/19	58
Total series *	8/20	24/38	32/58	55
Mean life span, yr.	4.0	3.4	3.6	
3 to 14 yr. survival *	4/15	12/20	16/35	46
Mean life span, yr.	4.8	5.2	5.0	
5 to 14 yr. survival *	3/10	5/9	8/19	42
Mean life span, yr.	5.9	7.6	6.7	

* As of last visit prior to July 1, 1950.

TABLE 12. *Chronic Granulocytic Leukemia: Summary of Representative Results of Therapy*

Authors	Report Date	Treatment	Fraction Surviving	%	Mean Survival, Months: Before Treatment	Mean Survival, Months: After Treatment	Mean Survival, Months: Total	Mean Survival, Years Total
Minot and others [10a]	1924	0	0/52	0	16.8	19.2	36	3.04
		Local radium	0/78	0	16.8	23.2	40	3.50
Hoffman and Craver [10b]	1931	Local roentgen rays to spleen or spleen and long bones plus 4 long-lived patients *	0/71 0/75	0 0	9 17	32 30	41 47	3.36 3.93
Wintrobe and Hasenbush [10c]	1939	Local irradiation, 29; potassium arsenite solution, 8	0/23	0 †	14 †	20	34	2.79
Pascucci [10d]	1942	.....	3/64	5	....	....	..	2.5
Reinhard and others [10e]	1946	P^{32} + roentgen rays and P^{32}	18/39	46	24.5	12.7	37.2	3.10
		P^{32} only *	11/19	58	22	11.2	33.2	2.77
Wintrobe and Huguley [10f]	1948	HN_2 ‡ and HN_2 + roentgen rays or urethan	7/11	64	25.3	11.2	36.5	3.04
Lawrence and others [10g]	1948	P^{32} + P^{32} and roentgen rays	21/129	16	....	....	....	3.7
		P^{32} only *	8/34	24	....	....	....	< 3.5
Osgood	1950	Titrated, regularly spaced total body irradiation	8/20	40	26.4	21.9	48.3	4.03

* Calculated from data given.
† Time before therapy calculated from 36 cases; time after therapy calculated from 23 cases dead; thus, fraction surviving of total series is 13/36, or 36 per cent.
‡ HN_2 signifies nitrogen mustard therapy.

TABLE 13.—*Chronic Lymphocytic Leukemia: Summary of Representative Results of Therapy*

Authors	Report Date	Treatment	Fraction Surviving	%	Mean Survival, Months: Before Treatment	Mean Survival, Months: After Treatment	Mean Survival, Months: Total	Mean Survival, Years Total
Minot and Isaacs [10h]	1924	0	0/30	0	16.8	23.2	40.0	3.33
		Local radium	0/50	0	16.8	25.0	41.8	3.53
Wintrobe and Hasenbush [10c]	1939	Local roentgen rays or radium, 22; potassium arsenite solution, 5	0/23	0 *	15 *	13	28	2.33
Bethell [10i]	1942	Local roentgen rays to spleen or long bones	0/18	0	29.2	23.4	52.6	4.3
Pascucci [10d]	1942	Local roentgen rays (all but 2 cases)	9/64	14	....	....	....	2.8
Reinhard and others [10e]	1946	P^{32} + P^{32} and roentgen rays	14/30	47	....	....	....	2.53
		P^{32} only †	10/21	48	13.9	10.5	24.4	2.03
Wintrobe and Huguley [10f]	1948	HN_2 ‡ (8 had roentgen rays or urethan)	7/14	50	21.6	7.7	29.3	2.44
Lawrence and others [10j]	1949	P^{32} only + P^{32} and roentgen rays	22/97	23	....	....	....	4.5
		P^{32} only †	14/41	34	....	....	....	< 4.12
Osgood	1950	Titrated, regularly spaced total body irradiation (1 had potassium arsenite solution)	24/38	63	24.0	16.3	40	3.36

* Time before therapy calculated from 35 cases; time after therapy calculated from 23 cases dead; thus, fraction surviving of total series is 12/35, or 34 per cent.
† Calculated from data given.
‡ HN_2 signifies nitrogen mustard therapy.

or after urethan administration, or both. Of these 34 cases the fraction surviving at the time of the report was 15/34, or 44.1 per cent, with a mean duration after urethan therapy was started of 8.9 months. However, the mean period of observation had been only eight months (0.5 to 21), which is too short a time to justify a final appraisal of this therapy. The duration before therapy varied from one to 60 months, but the mean is not stated.

Leucutia [13] concluded from a review of the literature up to 1934 that

> The prolongation of the average life duration is likewise rather insignificant, perhaps with ⅓ to ¼ of the natural expectancy, which is considered to be about 3½ years in the chronic forms of both the lymphatic and the myelogenous type. The symptomatic improvement, however, is remarkable and it is believed that the efficiency of the patient is increased at least 60% throughout the major part of the duration of the disease.

Paterson and her associates [12] reported on 19 patients with chronic leukemic lymphocytic leukemia, three with the acute disease, three with the subacute disease and one a leukemic patient, making a total of 26 patients treated with urethan. Of the 19 patients having chronic leukemic leukemia, 12 received roentgen therapy before or after the urethan treatment. Of these 19 the fraction surviving was 10/19, or 52.6 per cent, with a mean duration after urethan therapy was begun of 8.1 months. However, the mean duration of observation after therapy was only 6.5 months (0.5 to 18). The duration before therapy varied from one month to six years, but the mean is not stated.

Videbæk [14] reported 57 cases of chronic lymphocytic leukemia and 19 cases of acute "lymphosarcoma" cell leukemia treated at the Radium Center in Copenhagen, Denmark, between 1930 and 1945. Twenty-one of these patients had leukocyte counts between 2,000 and 20,000 per cubic millimeter. The average duration of life after onset of symptoms in the 57 chronic cases was 2.8 years. About 50 per cent of the entire group of 76 patients were dead at two years. One patient lived 10 years.

LIMITATIONS OF THE METHOD AND OF THE DATA PRESENTED

There is nothing to suggest that the described method is in any sense a cure of leukemia. While many patients have died of intercurrent diseases, many have died of leukemia during the course of this therapy. The usual mode of death is that typical of an acute leukemia, as is commonly seen in the terminal phase of chronic leukemias treated by other methods. Just before death it is usual to note the development of hemorrhagic phenomena of the thrombocytopenic type and a rising leukocyte count, notwithstanding increasing dosage and shorter intervals (see fig. 2). The same course is observed in those patients with lymphocytic leukemia who die of the leukemia; for example, a patient, case CLL 5 (1), entered the hospital for the first time, and had his first transfusion in 14 years of leukemic life, three weeks before death, with the typical picture of an acute leukemia and with uncontrollable bleeding.

The data do not permit a conclusion concerning how much of the improvement in longevity and efficient life is due to the psychotherapy,[4] how much to the dietary

13. Leucutia, T.: Irradiation in Lymphosarcoma, Hodgkin's Disease and Leukemia (A Statistical Analysis), Am. J. M. Sc. **188**:612-623 (Nov.) 1934.

14. Videbaek, A.: Do Malignant Lymphomas Represent Varying Differentiation of the Same Growth? Acta hæmatol. **2**:201-212 (Aug.) 1949.

regimen, how much to the improved antibiotics now available and how much to this method of giving irradiation, but it seems certain that each of these was a factor in the results.

This therapy does not solve the problem of treating the complication of acquired hemolytic anemia in the chronic lymphocytic leukemias, as can be seen in tables 9 and 10 and figures 5 and 6. Possibly the combination of pituitary adrenocorticotropic hormone (ACTH) or cortisone with splenectomy may solve this problem. The single patient, case CLL 38 (15), in this series who underwent splenectomy has continued to show active hemolysis. One other patient who had had previous urethan therapy and so was not included in this report responded to splenectomy. The other patients with acquired hemolytic anemia remained so critically ill, notwithstanding multiple transfusions, that splenectomy seemed unjustified.

Aside from the patients with acquired hemolytic anemia, few patients required blood transfusions or hospitalization because of leukemia in the interval between two months after therapy was started and two months before death.

Titrated, regularly spaced, total body irradiation will not reduce the size of enlarged, fibrotic spleens which have previously been treated with massive, intermittent, local roentgen therapy. No such cases are included in this report. In all the patients herein reported on who lived more than three months, spleens were reduced to within 1 or 2 cm. of the costal margin, most of them to above the costal margin. This may require three to four months, but they do not again enlarge until the terminal phase of the disease. While there is no contraindication to the use of local roentgen irradiation in conjunction with this therapy if lymph nodes and spleen fail to decrease in size, local treatment was used for only two patients in this series. One patient, case CLL 5 (1), received local roentgen therapy, coned down over a submaxillary lymph node draining an abscessed tooth which had failed to respond to the spray roentgen therapy alone; it also failed to respond to the local treatment in repeated doses of 100 to 150 r. Another patient, case CLL I (5), also received local therapy to a group of cervical lymph nodes with no effect, after they had failed to respond to titrated, regularly spaced, total body irradiation. Aside from the two patients with granulocytic leukemia who moved away, no other patients received local treatment after spray roentgen or P^{32} therapy was instituted.

The data presented for this series may be misleading if results of spray roentgen and P^{32} therapy are compared, unless allowance is made for the fact that all patients seen prior to Jan. 1, 1947 were treated by total body roentgen irradiation and all patients seen subsequent to that date have been treated with P^{32}. Naturally, the roentgen-treated patients have had time to accumulate a longer life span. It is not the purpose of this paper to compare the relative merits of the two methods of giving total body irradiation, although it is my impression that P^{32} has definite advantages over the total body roentgen therapy when adequate facilities and staff for administration and standardization are available. The advantages of P^{32} therapy are a definite, selective localization in the involved leukemic cells[7d]; control of the accuracy of dosage by the hematologist himself; the option of giving a larger dose in terms of rems (roentgens equivalent man) to the involved cells without producing radiation sickness, and the greater intervals between visits which the more prolonged action of P^{32} therapy makes possible.

Slight nausea has been observed by some patients receiving 25 r of total body roentgen therapy, and at 30 r nearly all patients have radiation sickness. Doses of P^{32} totaling many more rems have been given with no signs of radiation sickness until a dose of 100 microcuries per kilogram of body weight has been exceeded. No other untoward effects of ionizing radiation have been observed in this series of patients.

The reason for selecting a leukocyte level of less than 30,000 per cubic millimeter for recording the time in which the leukocyte count was under control should be stated. In the early phase of this work the leukocyte range of 15,000 to 25,000 per cubic millimeter was selected as the level at which to aim, to allow greater leeway against overtreatment. As skill with the method increased, this was changed to the range of 10,000 to 20,000. It is suggested that others who wish to utilize this method of treatment aim for leukocyte counts of 15,000 to 25,000 per cubic millimeter while they are developing skill with the method.

The figures presented should not be interpreted as representing the death rate due to leukemia with this treatment because several of the deaths were due to entirely unrelated diseases while the leukemia was under good control. In some of the patients death occurred too soon after therapy was started for the therapy to have had any influence on the leukemia. The results reported should, therefore, be interpreted as the fraction surviving and the total life span after onset of leukemia for the designated period of observation in chronic leukemic patients of this sex and age group. The data are so reported that those who wish may calculate the leukemic deaths after adequate therapy. However, there are great difficulties in interpretation if any selection whatsoever is made. There is a definite need for more data on total life spans of leukemic patients, irrespective of the cause of death, to permit comparison with the actuarial figures for the general population of the corresponding age and sex group.

SUMMARY

The method of titrated, regularly spaced, total body irradiation for the treatment of the chronic leukemias is described.

Every previously untreated patient with chronic leukemic granulocytic or chronic leukemic lymphocytic leukemia referred between 1941 and Dec. 30, 1949 was treated by this method and is reported on in this paper. The status of each patient as of the last visit prior to July 1, 1950 is reported.

The exact status of every patient started on this therapy is known.

The results of the therapy are presented in figures 4, 5 and 6 and tables 8 to 13. The data presented include death and disability from all causes. Of the 58 patients—20 with chronic leukemic granulocytic leukemia ranging in age from 3 to 71 years and 38 with chronic leukemic lymphocytic leukemia ranging in age from 27 to 81 years—32 are living at the time of this report. The mean duration of life from onset of the disease is 3.6 years for the total series, 4.0 years for those with granulocytic leukemias and 3.4 years for those with lymphocytic leukemia, of whom 18 were first seen since Jan. 1, 1949. Over 80 per cent of the total 208 years of leukemic life in this series of patients has been spent in essentially normal living.

These results appear to justify comparative trial of the method by other investigators.

The aid of the staff of the Division of Experimental Medicine of the University of Oregon Medical School made this work possible.

Dr. Arthur J. Seaman, Assistant Professor of Medicine, Dr. Jonah G. Li, Instructor in Medicine, and the residents in experimental medicine—Drs. Irvin Voth, Robert Koler and Thomas Stack—aided in the care of patients and compiling of records. Mr. Harold Tivey, biophysicist, standardized all P^{32} used and supervised safety standards. Miss Margret E. Hughes, research associate, prepared figures 4, 5 and 6 and edited the manuscript. The various secretaries, medical technologists, student assistants and laboratory aides, who have worked in the Division of Experimental Medicine since 1941, all contributed much to making this publication possible.

STUDIES ON ANTIBIOTIC SYNERGISM AND ANTAGONISM

The Interference of Chloramphenicol with the Action of Penicillin

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THE DYNAMICS of antimicrobial action are known to some extent for the "older" antibiotics, particularly penicillin. Data are being accumulated at present on the "newer" antibiotics, aureomycin, chloramphenicol and terramycin. Relatively little information, however, is available on the results of simultaneous action of two or more antibiotics. Such basic information is desirable particularly in view of the increasing trend for multiple antibiotic therapy in medical practice.

Two antibiotics acting simultaneously might be additive, synergistic, antagonistic or without any effect on each other. This spectrum of possible combinations has been shown to exist for various sulfonamides [1] and has been suggested for antibiotics.[2] Synergistic effects have been demonstrated for combinations of penicillin and streptomycin in their action against enterococci in vitro [3] and against enterococcic human infections.[4] In some other infections (e. g., brucellosis) it has also been shown that combinations of antibiotics can achieve results unobtainable with any single drug.[5]

From the Division of Bacteriology, University of California School of Medicine.

This study was supported in part by a grant from the Research Committee of the University of California School of Medicine.

1. Schweinburg, F. B., and Rutenburg, A. N.: In Vitro Sensitivity of Bacteria to Sulfonamide Combinations as Compared to Single Sulfonamides, Proc. Soc. Exper. Biol. & Med. **74**:480-483 (July) 1950.

2. Spicer, S.: Bacteriologic Studies of the Newer Antibiotics: Effect of Combined Drugs on Microorganisms, J. Lab. & Clin. Med. **36**:183-191 (Aug.) 1950.

3. (*a*) Jawetz, E.; Gunnison, J. B., and Coleman, V. R.: The Combined Action of Penicillin with Streptomycin or Chloromycetin on Enterococci in Vitro, Science **111**:254-256 (March 10) 1950. (*b*) Gunnison, J. B.; Jawetz, E., and Coleman, V. R.: The Effect of Combinations of Antibiotics on Enterococci in Vitro, J. Lab. & Clin. Med. **36**:900-911 (Dec.) 1950.

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5. Herrell, W. E., and Barber, T. E.: The Combined Use of Aureomycin and Dihydrostreptomycin in the Treatment of Brucellosis, Proc. Staff Meet., Mayo Clin. **24**:138-145 (March 16) 1949.

It has been reported previously that in vitro and in certain experimental infections chloramphenicol, aureomycin or terramycin may interfere with the antibacterial action of penicillin.[6] The simultaneous administration of two antibiotics thus results in a reduction of over-all antimicrobial effect. This phenomenon has been termed "antibiotic antagonism." The present paper reports more detailed studies dealing with the antagonism of chloramphenicol and penicillin in the test tube and in experimental infections of mice.

MATERIALS AND METHODS

Bacteria.—Two varieties of organisms were employed. One was a beta hemolytic Streptococcus pyogenes, group A, type 3, strain C 203, originally obtained from Dr. H. Eagle, and used in most experiments described here. The other was a Klebsiella pneumoniae, strain A-D, supplied by Dr. Edith R. Jackson. The virulence of both organisms was kept at high level by frequent passage through mice. The L. D_{∞} for mice inoculated intraperitoneally was 60 to 100 organisms of the Streptococcus and 100 to 250 organisms of the Klebsiella.

Mediums.—The broth used contained 20 Gm. of proteose no. 3 peptone (Difco), 0.5 Gm. of glucose, 5 Gm. of sodium chloride and 5 Gm. of disodium phosphate in 1,000 ml. of distilled water (*pH 7.2*). The agar medium had the same base plus 15 Gm. of agar per liter. The agar plates used for estimating the numbers of viable streptococci also contained 2 per cent sheep blood and 0.5 per cent penicillinase solution (bacto-penase,® Difco).

Antibiotics.—Commercial crystalline potassium or sodium penicillin G was dissolved in sterile saline solution prior to each test to make solutions of desired strength. Crystalline chloramphenicol was supplied by Dr. G. Rieveschl, of Parke Davis & Co., Detroit (chloromycetin,® synthetic, lots 131340 and 134006). It was dissolved in saline solution to make solutions containing 4 mg. per milliliter, which were sterilized by Seitz filtration and stored at 4 C. for several weeks without loss of potency. Final dilutions were prepared freshly for each test.

Method for in Vitro Tests.—Final dilutions of the antibiotics were freshly prepared in broth in a volume of 19 ml. and inoculated with 1 ml. of an 18 hour broth culture containing 10^7 to 10^8 bacteria per milliliter. All tubes were incubated at 37 C., and samples of 0.5 ml. were removed at intervals for the estimation of the number of viable bacteria by serial dilution and plate counts. Control experiments indicated that two to three fold differences in final counts of viable bacteria might occur as chance results with this technic. Consequently only tenfold (1.0 log) or greater differences in counts were considered significant.

Method for in Vivo Tests.—White Swiss mice weighing approximately 20 Gm. each from a heterozygous stock were used in all experiments in groups of 15 to 30 animals. Cultures of bacteria (streptococci) were grown in 5 per cent sheep blood broth at 37 C. for 18 hours. The animals were infected by the intraperitoneal injection of 0.2 ml. of a 10^{-4} dilution of culture containing approximately 100 L. D_{∞}. Most untreated animals died within three days and all within five days after infection. Antibiotics were administered subcutaneously or intraperitoneally in a volume of 0.2 ml. in the doses and at the time shown in the protocols. The first treatment was always administered one to four hours after the infecting injection. The animals were observed for 10 days and deaths recorded. Calculation of L. D_{∞} and C. D_{∞}[7] was according to the method of Reed and Muench.[8] Differences in the death rates of groups

6. (*a*) Footnote 3. (*b*) Jawetz, E., and Speck, R. S.: The Joint Action of Penicillin with Chloramphenicol on an Experimental Infection of Mice, Proc. Soc. Exper. Biol. & Med. **74**:93-96 (May) 1950. (*c*) Gunnison, J. B.; Coleman, V. R., and Jawetz, E.: Interference of Aureomycin and of Terramycin with the Action of Penicillin in Vitro, ibid. **75**:549-552 (Nov.) 1950.

7. C. D_{∞} signifies median curative dose.

8. Reed, L. J., and Muench, H.: A Simple Method of Estimating 50 Per Cent Endpoints, Am. J. Hyg. **27**:493-497 (May) 1938.

of animals were considered significant for the demonstration of antibiotic antagonism only if they exceeded 30 per cent. Occasional mice were autopsied, and the heart blood was cultured to ascertain the cause of death. Pure cultures of the infecting organisms were always recovered.

RESULTS

1. *Demonstration of the Interference of Chloramphenicol with Penicillin.*—After initial observation of the antagonism of chloramphenicol and penicillin in their action against enterococci in vitro,[3] the same experimental approach was extended to Str. pyogenes. Again it was found that chloramphenicol interfered significantly with the early bactericidal effect of penicillin. The type of interference observed in vitro with a wide range of concentrations and proportions of drugs is illustrated in chart 1. Similar reactions were encountered with K. pneumoniae, though with different concentrations of the two drugs, as discussed below.

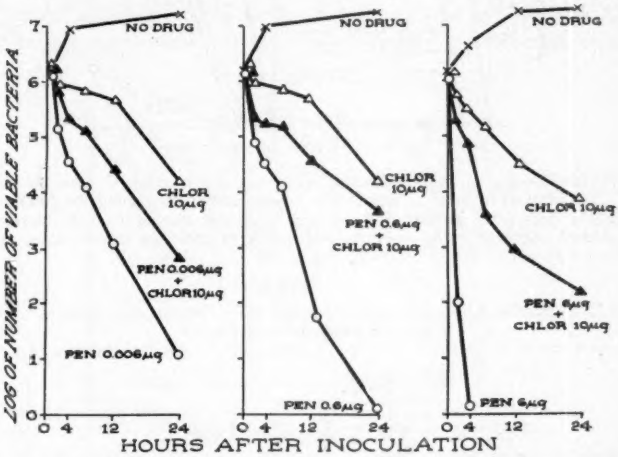

Chart 1.—Interference of chloramphenicol with early bactericidal effect of penicillin on Streptococcus C 203 in vitro. Graphs show ability of 10 micrograms per milliliter of chloramphenicol to interfere with action of penicillin in concentrations of 0.006 to 6.0 micrograms per milliliter.

Chloramphenicol in test tube experiments interfered most markedly with the early bactericidal action of penicillin but did not prevent the ultimate sterilization of the culture by the antibiotics. It was questionable, therefore, whether this drug antagonism would occur in vivo. In experimental streptococcic infections of mice, however, the phenomenon was demonstrated without any difficulty, when both drugs were administered intraperitoneally and within a few minutes of each other.[6b] With penicillin injected subcutaneously and chloramphenicol intraperitoneally, groups of animals receiving both drugs likewise had a much higher death rate than those treated with penicillin only. Representative experiments illustrating minimal and maximal antagonism in vivo with Streptococcus C 203 are shown in chart 2. These results indicate that the interference of chloramphenicol with the early bactericidal action of penicillin in vitro had its counterpart in vivo, where chloramphenicol interfered with the curative action of penicillin.

2. *Dose Relationship in the Antagonism of Chloramphenicol and Penicillin.*—Survey experiments to delineate the drug concentrations which would result in interference of chloramphenicol with pencillin indicated that the range of each drug involved in interference depended on the test organism. The results obtained with Streptococcus C 203 and a strain of Klebsiella are summarized in table 1.

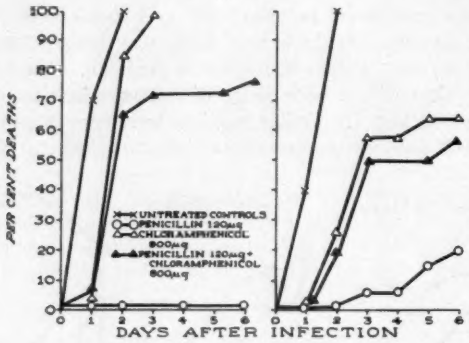

Chart 2.—Interference of chloramphenicol with therapeutic effect of penicillin on Streptococcus C 203 infection in mice. Results of two experiments illustrating maximal (left) and minimal (right) degrees of interference observed when 800 micrograms of chloramphenicol was administered intraperitoneally and 120 micrograms of penicillin subcutaneously one hour after infection with 100 L. $D._{50}$ of Streptococcus C 203.

TABLE 1.—*Influence of Drug Concentration and Dose Relationship on Occurrence of Antibiotic Antagonism in Vitro* *

Test Organism	Penicillin, Micrograms/Ml.	Chloramphenicol, Micrograms/Ml. Time Necessary to Reduce Viable Bacteria by 99.9% (Hours)	1	2	5	10	25	100
			> 144	96 to 144	48	24 to 48	24	12 to 18
		Hours						
Str. progenes C 203	0.006	12 to 18	—	0	+	+	0	++
	0.012	8 to 12	—	+	0	+	0	0
	0.06	8 to 12	—	+	+	+	+	++
	0.6	6 to 8	—	0	0	++	0	++
	6.0	2 to 4	—	0	0	+	+	+
	60.0	< 2	0	0	0	—	0	—
		Hours	> 144	8 to 12	6 to 8		6 to 8	
K. pneumoniae A-D	6.0	6 to 8	0	+	+	0	—	0
	12.0	3 to 6	++	+	+	0	—	0
	30.0	2 to 4	0	0	+	0	—	0

* Minus sign indicates no significant interference (less than 1.0 log); +, significant interference of 1.0 to 2.5 logs (i. e., the log of the number of viable bacteria was on the average 1 to 2.5 higher in the presence of two drugs than with penicillin alone during the first 12 hours of incubation); ++, significant interference of more than 2.5 logs, and 0, test not performed with this combination.

It appears that the range of penicillin concentrations antagonized by a single chloramphenicol concentration (e. g., 10 micrograms per milliliter) may be as wide as a thousandfold (0.006 to 6.0 micrograms per milliliter with Streptococcus C 203). The range of chloramphenicol concentrations interfering with a single

concentration of penicillin (e. g., 0.06 microgram per milliliter) may likewise be wide (fiftyfold, 2 to more than 100 micrograms per milliliter with Streptococcus C 203).

The wide ranges of the two drugs that result in interference make it unlikely that this phenomenon could be attributed to simple chemical inactivation of one drug by the other. This impression is confirmed by the finding that interference resulted in the mixture of 0.06 microgram per milliliter of penicillin and 25 micrograms per milliliter of chloramphenicol with Streptococcus C 203, but not with Klebsiella. Conversely, there was interference between 1 microgram per milliliter of chloramphenicol and 6.0 micrograms per milliliter of penicillin with Klebsiella, but not with Streptococcus as test organism (table 1; chart 3).

The occurrence of antibiotic antagonism was related to the biologic activity of the substances. Chloramphenicol was incapable of interfering with penicillin when it was present either in concentrations below bacteriostatic levels or in concentrations having considerable activity as measured by the reduction of the viable

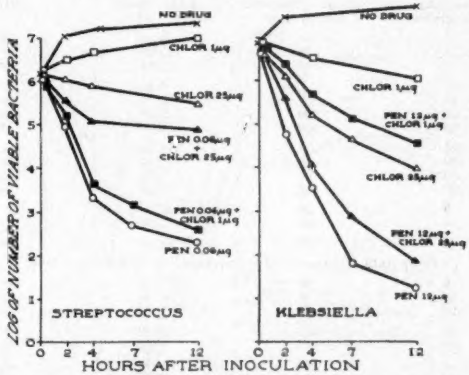

Chart 3.—Effect of different concentrations of chloramphenicol and penicillin on occurrence of antibiotic antagonism with different organisms in vitro. One microgram per milliliter of chloramphenicol interferes with 12.0 micrograms per millimeter of penicillin in the case of Klebsiella, but not with 0.06 microgram per milliliter of penicillin with Streptococcus as the test organism. Twenty-five micrograms per milliliter of chloramphenicol interferes with 0.06 microgram per milliliter of penicillin in the case of the Streptococcus but not with 12.0 micrograms per milliliter of penicillin with Klebsiella as the test organism.

bacterial population by 99.9 per cent in a few hours. If a very large excess of penicillin was present (e. g., 10,000 times the minimum bactericidal concentration), interference was not observed with any amount of chloramphenicol.

The effect of dosage relationships on the occurrence of antibiotic antagonism was also studied in vivo in a streptococcic (strain C 203) infection of mice. Death of experimental animals was used as the sole criterion for drug efficiency or interference. No attempt was made to correlate blood levels of the drugs to in vivo antibiotic antagonism because the lack of close relationship between blood levels and therapeutic effects has long been recognized.[9]

9. (*a*) Jawetz, E.: Dynamics of the Action of Penicillin in Experimental Animals, Arch. Int. Med. **77**:1-15 (Jan.) 1946. (*b*) Eagle, H.: Speculations as to the Therapeutic Significance of the Penicillin Blood Level, Ann. Int. Med. **28**:260-278 (Feb.) 1948.

The trends seen in experiments with single doses of each drug (table 2) administered intraperitoneally within a few minutes of each other one hour after infection can be summarized briefly. With minimal curative doses of penicillin (e.g., 6 to 30 micrograms, 2 to 10 $C.D._{50}$), small doses of chloramphenicol (50 micrograms) produced maximal interference that could not be increased by raising the chloramphenicol dose four to sixteen fold. With larger doses of penicillin (20 to 40 $C.D._{50}$), the same small amounts of chloramphenicol (50 micrograms) produced only slight interference, whereas larger amounts resulted in progressively greater antagonism.

When penicillin doses of increasing size were combined with any given dose of chloramphenicol, the death rates progressively decreased. This again suggested

TABLE 2.—*Influence of Dose Relationship on Occurrence of Antibiotic Antagonism in Vivo*

Drugs		Mice	
Penicillin, Micrograms	Chloramphenicol, Micrograms	Dead/Total	% Dead
6	0	3/26	12
6	50	11/16	68
6	800	11/16	68
30	0	2/20	10
30	50	13/20	65
30	200	12/20	60
30	800	12/20	60
120	0	1/26	4
120	50	12/35	34
120	200	8/20	40
120	800	18/36	50
0	50	13/16	81
0	800	17/30	57
0	0	44/44	100
Same Data Rearranged for Constant Chloramphenicol Dose			
6	50	11/16	68
30	50	13/20	65
120	50	12/35	34
30	200	12/20	60
120	200	8/20	40
6	800	11/16	68
30	800	12/20	60
120	800	18/36	50

One hour after infection with Streptococcus C 203 (100 L. $D._{50}$) groups of mice were given intraperitoneal injections of a single dose of one or both drugs.

an effect of excess penicillin not antagonized by the fixed dose of chloramphenicol, similar to the in vitro effect noted above.

The experiments on dose relationships were then extended to multiple dose schedules, resulting in significant tissue levels of the drugs for approximately 10 to 12 hours. In addition, the sites of administration of the drugs were separated, penicillin being administered subcutaneously and chloramphenicol intraperitoneally. Chart 4 shows the results of an experiment in which 18, 36 or 90 micrograms of penicillin in three equal portions, administered subcutaneously every four hours, were given to groups of mice also receiving 200 micrograms of chloramphenicol intraperitoneally every four hours.

The results of these three dose experiments parallel those shown earlier for single dose relationships. Antibiotic antagonism was readily apparent. Again the

magnitude of interference diminished as penicillin in excess of the minimal curative dose was added to the chloramphenicol. Interference by 600 micrograms of chloramphenicol with a total dose of 18 micrograms of penicillin (approximately 8 $C.D._{.50}$) was pronounced, whereas with 90 micrograms of penicillin (approximately 40 $C.D._{.50}$) antagonism was no longer demonstrable.

3. Time Relationship in the Antagonism of Chloramphenicol with Penicillin.—The occurrence of antibiotic antagonism in vivo with multiple dose schedules of both drugs suggested that simultaneous administration of penicillin and chloramphenicol was not necessary for the demonstration of the phenomenon. Conse-

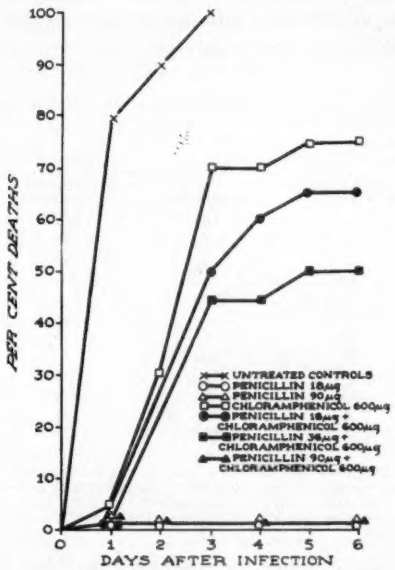

Chart 4.—Interference of chloramphenicol with therapeutic effect of penicillin on Streptococcus C 203 infection in mice. Levels of both drugs were maintained by injecting 6, 12 or 30 micrograms of penicillin subcutaneously and 200 micrograms of chloramphenicol intraperitoneally at two, six and 10 hours following infection with 100 L. $D._{50}$ of Streptococcus C 203. The more penicillin was administered with a constant amount of chloramphenicol, the lower the death rate (i. e., the less interference).

quently, studies were undertaken to define more accurately the interval between injections of the drugs which would still permit interference to occur.

The protocol of one such experiment is shown in table 3. Antagonism was demonstrated if the administration of chloramphenicol preceded that of penicillin by one-half to one hour, but not if two hours elapsed or if penicillin was injected first. Past experience indicated [10] that under the conditions of this experiment

10. Jawetz,[9a] Thompson, P. E.; Dunn, M. C., and Winder, C. V.: Comparison of the Actions of Chloramphenicol (Chloromycetin®) and Penicillin G Against Relapsing Fever in Mice, J. Infect. Dis. **86**:110-121 (March-April) 1950.

penicillin was present in the tissues for more than one-half hour and chloramphenicol for more than one hour in significant concentrations. Consequently, speed and differences in absorption and excretion of the drugs do not entirely account for the observed differences. The data are, however, in agreement with the hypothesis that antagonism could be demonstrated only if chloramphenicol came in contact with the micro-organisms prior to, or simultaneously with, penicillin, but not if that drug exerted its effects first.

In vitro experiments yielded results that were also compatible with this hypothesis. When populations of Streptococcus C 203 were exposed to chloramphenicol (10 micrograms per milliliter) for one or two hours prior to the addition of penicillin (0.6 micrograms per milliliter) interference was marked, and the population curve followed that noted for chloramphenicol alone. Conversely, when penicillin

TABLE 3.—*Influence of Time Dose Relationship on Occurrence of Antibiotic Antagonism in Vivo*

Drug Administered, Time After Infection (Hr.)		Mice		
Penicillin, 120 Micrograms	Chloramphenicol, 800 Micrograms	Dead/Total	Per Cent Deaths	Interference Effect
2	..	1/15	7	..
..	2	10/15	67	..
2	2	6/15	40	+
2	2½	2/15	13	—
2	3	2/15	13	—
2	4	1/15	7	—
2½	2	7/15	47	+
3	2	6/15	40	+
4	2	1/15	7	—
4	..	3/15	20	..
..	4	9/15	60	..
4	4	8/15	53	+

Mice were infected with Streptococcus C 203 (100 L. D.50) and at the times indicated in the chart 120 micrograms of penicillin in 0.2 ml. was injected subcutaneously or 800 micrograms of chloramphenicol in 0.2 ml. was injected intraperitoneally. The interference effect was denoted as positive (+) if the difference in death rate between groups of animals receiving two drugs and those receiving penicillin alone exceeded 30 per cent.

acted for one or two hours before the chloramphenicol was introduced, the initial rapid drop in viable bacteria due to penicillin was followed by only a temporary flattening of the curve following the addition of chloramphenicol. In the latter instance interference was slight.

4. *The Ability of Synergistic Drugs to Overcome Antibiotic Antagonism.*—It is known that both streptomycin and bacitracin are synergistic with penicillin against a number of micro-organisms.[11] These drugs, in concentrations which alone have little demonstrable effect on the test organism, are capable of greatly increasing the rate of bactericidal action of penicillin. Since the interfering effect

11. Spicer.[2] Gunnison and others.[3b] Hunter.[4b] Bachman, M. C.: In Vitro Studies on Possible Synergistic Action Between Penicillin and Bacitracin, J. Clin. Investigation **28**:864-866 (Sept., pt. 1) 1949. Eagle, H., and Fleischman, R.: Therapeutic Activity of Bacitracin in Rabbit Syphilis and Its Synergistic Action with Penicillin, Proc. Soc. Exper. Biol. & Med. **68**:415-417 (June) 1948.

of chloramphenicol on the action of penicillin appears to be chiefly a decrease in the early bactericidal effect, it was of interest to determine whether streptomycin or bacitracin could overcome this interference.

It was shown in a series of tests that this was indeed the case. With the use of Streptococcus C 203 as the test organism, both bacitracin (0.005 unit per milliliter) and streptomycin (5 micrograms per milliliter) were synergistic with penicillin and were capable of overcoming the antagonistic effects of chloramphenicol (10 to 200 micrograms per milliliter; chart 5). The population curve resulting from the added effects of one drug synergistic with penicillin and another drug antagonistic to penicillin appears to approximate the arithmetic sum of the individual effects. Preliminary experiments in mice indicate that streptomycin in vivo also can partially overcome the interference of chloramphenicol with the therapeutic effect of penicillin. This effect is being further explored.

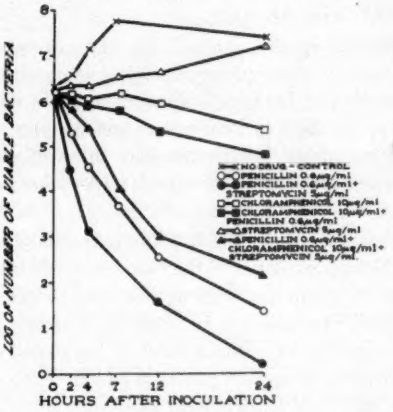

Chart 5.—Ability of streptomycin to overcome interference of chloramphenicol with action of penicillin on Streptococcus C 203 in vitro.

COMMENT

The antagonism of chloramphenicol and penicillin is not a mutual phenomenon but appears to be an interference of chloramphenicol with the bactericidal action of penicillin. The reverse, i. e., interference of penicillin with the action of chloramphenicol, has not been demonstrated to date.

The data presented in this paper permit speculation on the basis for this phenomenon. From the experiments on dosage relationships it is seen that antagonism could be demonstrated only when penicillin in effective concentrations in vitro or in vivo was mixed with relatively inactive amounts of chloramphenicol. Interference took place when chloramphenicol was present in bacteriostatic concentrations, or amounts giving a low (0 to 50 per cent) survival rate in mice, but could not be demonstrated in vitro either with very active concentrations of chloramphenicol or with concentrations without any bacteriostatic effect. Similarly, the phenomenon was greatly diminished or could not be demonstrated when

penicillin was present either in large excess or in amounts too small to have significant therapeutic activity. It is possible, of course, that these limitations are artificially imposed by the technics used and that more quantitative methods for the evaluation of antibiotic antagonism will remove them. However, as these same limitations have been encountered in other drug pairs, e. g., the antagonism between aureomycin and penicillin,[6c] for the time being, they may be considered valid.

The antagonism between chloramphenicol and penicillin could be explained by either of the following alternative mechanisms:

1. The two drugs interact chemically or physically in such a manner as to neutralize each other's actions.

2. One drug acts on the micro-organisms and modifies them in such a way as to reduce the susceptibility to the other drug. This possibility includes modifications in development, growth, division, multiplication and the enzymatic processes associated with them. It also includes the possibility that one drug competes for hypothetical "receptors" with the other.

All available evidence speaks against the first-mentioned mechanism. No support has been found for chemical or physical combination between the drugs, such as complex formation or binding.[12] Furthermore, the extremely wide ranges of drug concentrations resulting in interference and the pronounced differences in the proportions of drugs giving interference with different micro-organisms make it unlikely that molecular combination or complex formation accounts for antibiotic antagonism.

The second alternative suggests the hypothesis that antibiotic antagonism may be a function of the biologic activities of the two drugs. It is known that penicillin is bactericidal and has its greatest activity against micro-organisms in active growth and division, whereas chloramphenicol is chiefly a bacteriostatic agent. It can be postulated that the presence of chloramphenicol interferes with rapid microbial division and consequently with optimal penicillin effect. Support for this hypothesis can be found in the following experimental facts:

(*a*) Chloramphenicol is only antagonistic in concentrations that have some, though slight, bacteriostatic effect, whereas smaller, biologically inactive concentrations do not produce interference with penicillin.

(*b*) Chloramphenicol is antagonistic only if it reaches the micro-organisms prior to, or simultaneously with, penicillin but has little effect if penicillin acts first.

(*c*) The greatest antagonistic effect of chloramphenicol is observed early, when the bactericidal action of penicillin is maximal. Later the antagonism of chloramphenicol diminishes as the rate of bactericidal action of penicillin decreases.[8]

(*d*) The synergism of streptomycin (or bacitracin) with penicillin is based on an increase of the early bactericidal effects. Streptomycin is known to act on nonproliferating organisms which are not significantly affected by penicillin. The ability of the "synergistic" drugs (streptomycin and bacitracin) to overcome the

12. Dr. L. Strait, College of Pharmacy, University of California, studied ultraviolet absorption curves of penicillin, chloramphenicol and their mixtures over a wide range of concentrations and proportions and in various solvents. The results gave no evidence for physical or chemical combination of the drugs.

antagonism of chloramphenicol and penicillin suggests that both synergistic and antagonistic effects, occurring during the early stages of penicillin action, might have a common basis in modifications of the exposed bacteria.

Not readily alined with the hypothesis proposed above is the definite ability of excess amounts of penicillin to overcome chloramphenicol antagonism. Some form of mass action could, perhaps, explain this effect.

The demonstration of this new type of drug "incompatibility" in vitro and in experimental infections may have to be taken into account in future considerations of multiple antibiotic therapy. It is noteworthy that the drug concentrations exhibiting significant antibiotic antagonism encompass the range believed to occur in human body fluids and tissues with administration of therapeutic doses. No evidence exists to date, however, proving conclusively that this phenomenon may be encountered in the treatment of human infections with antibiotics, and no such suggestion is implied in this paper.

SUMMARY

Antagonistic effects between chloramphenicol and penicillin have been demonstrated in vitro with both gram-positive (Streptococcus) and gram-negative (Klebsiella) organisms and in vivo in a streptococcic infection of mice. The antagonism between the two drugs extends over wide ranges of concentrations of each drug but is limited by the degree of antimicrobial activity of the drugs. The phenomenon is observed in vivo when the drugs are given at different sites in either single or multiple injections. However, antagonism occurs only if chloramphenicol is given prior to, or simultaneously with, penicillin, not if penicillin is administered first. Drugs synergistic with penicillin, e. g., streptomycin or bacitracin, can overcome the antagonism between chloramphenicol and penicillin.

Evidence is presented to indicate that the phenomenon is not one of mutual antagonism between the two drugs but rather an interference of chloramphenicol with the early bactericidal, or therapeutic, effect of penicillin. The two drugs do not appear to interact in a physical or chemical way resulting in inactivation, but probably chloramphenicol modifies the characteristics of the bacterial population so as to make it less susceptible to penicillin action.

ANTISTREPTOLYSIN O RESPONSE FOLLOWING HEMOLYTIC STREPTOCOCCUS INFECTION IN EARLY CHILDHOOD

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AND
JOSEPH M. DI CAPRIO, M.D.
SAN FRANCISCO

HEMOLYTIC Streptococcus infections in human beings have been intensively studied during the last 20 years particularly because of the intimate association of these disorders with acute rheumatic fever.[1] The subjects of nearly all these investigations have been in one of two categories. One group has been composed of persons, usually children, in whom the rheumatic state or acute nephritis was already established.[2] The other has consisted of young adults, often military personnel, in whom detailed analyses of the natural history of acute streptococcic respiratory infection and its nonsuppurative sequelae have been made.[3]

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1. Swift, H. F.: The Etiology of Rheumatic Fever, Ann. Int. Med. **31**:715, 1950.

2. (*a*) Coburn, A. F., and Pauli, R. H.: Studies on the Immune Response of the Rheumatic Subject and Its Relationship to Activity of the Rheumatic Process: VI. The Significance of the Rise of Antistreptolysin Level in the Development of Rheumatic Activity, J. Clin. Investigation **14**:769, 1935. (*b*) Mote, J. R., and Jones, T. D.: Studies of Hemolytic Streptococcal Antibodies in Control Groups, Rheumatic Fever, and Rheumatoid Arthritis: I. The Incidence of Antistreptolysin "O," Antifibrinolysin and Hemolytic Streptococcal Precipitating Antibodies in Sera of Urban Control Groups, J. Immunol. **41**:35, 1941; (*c*) II. The Frequency of Antistreptolysin "O," Antifibrinolysin and Precipitating-Antibody Responses in Scarlet Fever, Hemolytic Streptococcal Infections and Rheumatic Fever, ibid. **41**:61, 1941; (*d*) III. The Magnitude of Antistreptolysin "O," Antifibrinolysin and Precipitating-Antibody Responses; Persistence of Antibodies, and Variations in Antistreptolysin "O" Curves in Scarlet Fever, Hemolytic Streptococcal Infections and Rheumatic Fever, ibid. **41**:87, 1941. (*e*) Taran, L. M.; Jablon, J. M., and Weyr, H. N.: Immunologic Studies in Rheumatic Fever: II. Antistreptolysin Patterns in Rheumatic Children, ibid. **53**:381, 1946.

3. (*a*) Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: The Etiology and Pathogenesis of Rheumatic Fever, Arch. Int. Med. **76**:131 (Sept.) 1945. (*b*) Rantz, L. A.; Randall, E., and Rantz, H. H.: Antistreptolysin "O": A Study of This Antibody in Health and in Hemolytic Streptococcus Respiratory Disease in Man, Am. J. Med. **5**:3, 1948. (*c*) Rothbard, S.; Watson, R. F.; Swift, H. F., and Wilson, A. T.: Bacteriologic and Immunologic Studies on Patients with Hemolytic Streptococcic Infections as Related to Rheumatic Fever, Arch. Int. Med. **82**:229 (Sept.) 1948. (*d*) Anderson, H. C.; Kunkel, H. G., and McCarty, M.: Quanti-

Surprisingly few studies have been made of the course and associated immunologic phenomena in group A Streptococcus infection in nonrheumatic infants and children, although the diseases caused by these organisms are unusual in civilian life in any age groups but these. Most important has been the report of Powers and Boisvert,[4] which clearly defined the changing pattern of Streptococcic infection with advancing age during early childhood and which will be discussed later in this paper. This work was done largely with patients sufficiently ill to require hospitalization, and no immunologic investigation was carried out.

One report has described the nature of the antistreptolysin O response in infants and older children and has indicated a striking difference between the two age groups.[5] Other immunologic studies have included children but have not been directed at an elucidation of the entire spectrum of hemolytic Streptococcus infection and its associated antibody phenomena in children of all ages.[6]

A continuing program was established three years ago to obtain detailed information in regard to the natural history of hemolytic Streptococcus infection in ambulatory children under 8 years of age. This report describes the antistreptolysin O response in a selected group of these children about whom adequate data were available and the period of observation was prolonged.

It should be borne in mind in considering these observations that work with ambulatory outpatients is accompanied with certain difficulties. Niceties of immunologic study, such as acute phase serums, may not be available because patients often do not visit the clinic until the disease has been established for some time. Similarly, clinical data or serum collections at a critical time during convalescence are often not obtained because the subjects fail to return to the clinic after the planned interval.

MATERIALS AND METHODS

Clinical Material.—Ambulatory children under 8 years of age attending the Pediatric Outpatient Clinics of Stanford University Hospitals and believed to be suffering from group A hemolytic Streptococcus respiratory infection, on the basis of appropriate clinical examination and recovery of these organisms in large numbers from the nasopharynx and from purulent material in ears or skin, were accepted for detailed investigation. Clinical and bacteriologic studies were repeated at various intervals, and serum was collected simultaneously and preserved in the frozen state.

Investigation has been continued for three years, and one or more group A Streptococcus infections has been observed in approximately 150 children. Fifty-eight of these have been selected for inclusion in this analysis because (1) actual infection of the respiratory tract could be established on clinical or immunologic grounds; (2) the time of onset of the acute process

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tative Antistreptokinase Studies in Patients Infected with Group A Hemolytic Streptococci: A Comparison with Serum Antistreptolysin and Gamma Globulin Levels with Special Reference to the Occurrence of Rheumatic Fever, J. Clin. Investigation **27**:425, 1948. (*e*) Kilbourne, E. D., and Loge, J. P.: The Comparative Effects of Continuous or Intermittent Penicillin Therapy on the Formation of Antistreptolysin in Hemolytic Streptococcal Pharyngitis, ibid. **27**:418, 1948.

4. Powers, G. F., and Boisvert, P. L.: Age as a Factor in Streptococcosis, J. Pediat. **25**:481, 1944.

5. Lippard, V. W., and Johnson, P.: Beta Hemolytic Streptococcic Infection in Infancy and in Childhood: I. Antifibrinolysin and Antistreptolysin Response, Am. J. Dis. Child. **49**:1411 (June) 1935.

6. Footnote *2b* to *d*. Wilson, M. G.; Wheeler, G. M., and Leask, M. M.: Antistreptolysin Content of Blood Serum of Children: Its Significance in Rheumatic Fever, Proc. Soc. Exper. Biol. & Med. **31**:1001, 1934. Gordon, J. E., and Janney, J. H.: Antistreptolysin Content of the Sera of Normal Infants and Children, J. Pediat. **18**:587, 1941.

could be accurately defined; (3) serial studies had been carried out over a long period and at sufficiently frequent intervals, and (4) possible or probable reinfection (except in six instances) by new types of group A streptococci had not occurred to obscure the immunologic phenomena under observation. None of the total group was excluded for reasons other than inadequacy of essential data or occurrence of reinfection.

Penicillin Therapy.—Penicillin was administered in certain cases in standard courses, consisting of daily injections of 300,000 units of procaine penicillin in aqueous suspension for five consecutive days of three doses at 48 hour intervals of the same amount of the drug suspended in oil and 2 per cent aluminum monostearate.

Bacteriologic Studies.—Cotton-tipped wood swabs were passed through the mouth and rubbed over the tonsils and nasopharynx under direct vision. Controlled studies revealed that the passage of wire swabs through the nose was an unsatisfactory technic for the recovery of group A streptococci from this area. Materials were obtained from the nose by inserting wire swabs approximately 4 cm. into the nasal ostiums and from the ears and skin in the usual way.

All swabs were streaked on two 10 per cent horse blood agar plates, one being prepared as a "streak pour plate" and incubated for 18 hours.

Isolated hemolytic streptococci were grouped and typed by precipitin technics.[7] The incidence of the various types isolated from this group of patients is presented in table 1. Untypable strains were recovered frequently.

Antistreptolysin O.—The concentration of antistreptolysin O in the collected serums was measured by a method previously described.[8]

TABLE 1.—*Incidence of Various Types of Hemolytic Streptococcus Isolated from Present Series of Patients*

Type	1	6	12	25	28	33	38	41	43	44	Untypable
Number.....	8	1	8	1	1	1	1	2	1	13	37

RESULTS

Three well defined patterns of antisteptolysin O response following group A hemolytic Streptococcus infection in childhood were discovered.

Pattern Group 1.—Thirteen children exhibited an exceedingly feeble antibody reponse. No measurable antistreptolysin (less than 12 units per milliliter) appeared in the serum of seven children followed 37 to 207 days (first seven cases in table 2). Infection was definite in every instance on clinical grounds; otitis media was present in five children and purulent rhinitis in two. Penicillin was administered early to four, late to two and not at all to one.

A peak antistreptolysin level of 12 units per milliliter was attained by six children (cases 8 to 13, table 2) followed 39 to 188 days. Infection was established by the presence of otitis media in four, pharyngitis and pyoderma in one and purulent sinusitis in one child. Penicillin was administered early to two children, late to two and not at all to two.

If these 13 children are considered together, the mean age was 14.3 and the extremes were 4 and 48 months. Only four were over 18 months of age and only two over 24 months old. The age distribution among this and two other antibody pattern groups is summarized in table 3.

7. Swift, H. F.; Wilson, A. T., and Lancefield, R. C.: Typing Group A Hemolytic Streptococci by M Precipitin Reactions in Capillary Pipettes, J. Exper. Med. **78**:127, 1943. Serums were supplied by the United States Public Health Service Communicable Disease Center, Chamblee, Ga.

8. Rantz, L. A., and Randall, E.: A Modification of the Technique for the Determination of the Antistreptolysin Titer, Proc. Soc. Exper. Biol. & Med. **59**:22, 1945.

Respiratory infections were present in all and were complicated by otitis media in seven, purulent rhinitis in three and pyoderma in one. Three children received no penicillin. The drug was given to six early in the course of the disease and to three during the second week.

Pattern Group II.—A second group of 18 was composed of children in whom an antibody response of varying degree occurred, the mean peak titer being 235 units per milliliter, and was followed by a rapid decline to low levels. The data for six in whom the peak level was 50 units per milliliter are presented in figure 1 *A*. All children in whom measurements were made at an appropriate time had attained a maximum titer within 30 days. The levels fell to 12 units in a mean time of 40.5

TABLE 2.—*Data in Thirteen Cases of Hemolytic Streptococcus Respiratory Infection in Which No Measurable or Very Little Antistreptolysin O Was Formed*

Case No.	Age, Mo.	Serum Obtained on Days *	Penicillin Therapy, Day Begun	Complications
1	4	11, 24, 45, 80, 143	None	Otitis media
2	20	6, 21, 42, 77	5	Purulent rhinitis
3	20	7, 55	6	Otitis media
4	8	9, 37	4	Otitis media
5	4	7, 21, 35, 152	7	Purulent rhinitis
6	48	16, 33, 47, 63, 112	16	Otitis media
7	5	13, 27, 46, 207	14	Otitis media
8	8	16, **24**, 45, 111	16	Otitis media
9	12	3, **12, 27**, 132	3	Otitis media
10	14	**13, 30, 57, 188, 370**	12	Otitis media
11	11	**12, 24, 45**	None	Otitis media
12	4	12, 21, **42, 49**	None	Purulent rhinitis
13	26	3, 14, **28**, 39	4	Pyoderma

* Boldface numbers indicate days on which serum containing 12 units of antistreptolysin per milliliter was obtained. No measurable antibody was demonstrated in any other instances.

TABLE 3.—*Age of Children in Three Antibody Pattern Groups at Onset of Infection*

Antibody Pattern Group	Age, Mo.													Mean Age, Mo.
	0 to 5	6 to 10	11 to 15	16 to 20	21 to 25	26 to 30	31 to 35	36 to 40	41 to 45	46 to 50	51 to 55	56 to 60	60 +	
I	3	3	3	2	0	1	0	0	0	1	0	0	0	14.3
II	0	0	5	1	2	1	1	2	0	0	2	1	3	36.7
III	0	0	1	0	0	1	0	1	2	0	4	3	9	57.9

days after the onset of the illness. The extremes were 23 and 76 days. Further serums were obtained 266, 314 and 265 days after the onset in three, and no measurable antistreptolysin O was present.

All these children had respiratory infections, complicated in two instances by otitis media. One received penicillin early and two not at all. The drug was given to the others after the peak of the antibody response was attained. The mean age of the group was 36.3 months.

Twelve additional cases were similar to those just described except for the fact that the maximum concentrations of antistreptolysin O were much higher (fig. 1 *B*). Rapid declines from peaks of 100 to 500 units per milliliter to low values of 12 units per milliliter occurred in 27 to 130 days. Two cases are included in which there were rapid falls in titer from very high levels to 50 units per milliliter in 122 and 160 days, respectively.

Respiratory infections were present in all these cases. Four were complicated by otitis media and two by suppurative cervical adenitis. Four patients received no penicillin, and six were given the drug after the peak of antibody response. The mean age was 36.8 months (table 3).

Pattern group II, in summary, was composed of 18 patients with hemolytic Streptococcus respiratory infection. A suppurative complication was present in eight. Six received no penicillin, and in nine it was given after maximum antibody levels had been attained during the second or third weeks of illness. The mean age was 36.7 months, but the extremes were 11 and 85 months (table 3). Five were infants less than 15 months old, and six were more than 50 months of age.

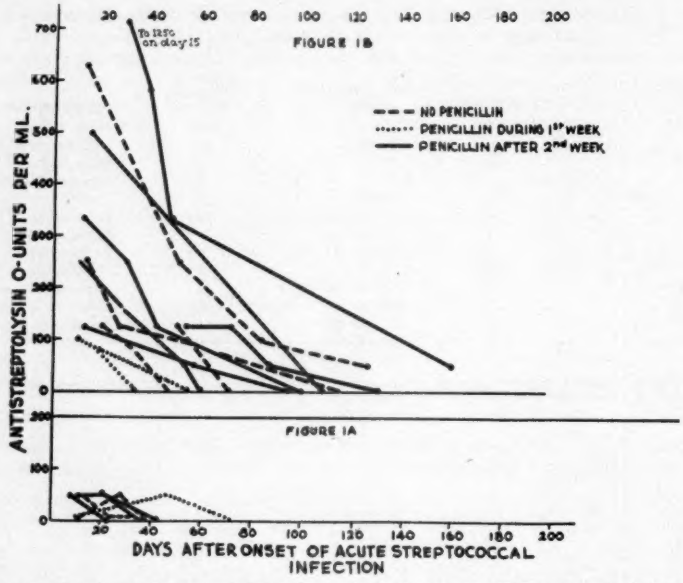

Fig. 1.—Graph showing pattern II antistreptolysin O response. This pattern is characterized by a rapid fall in serum antistreptolysin O concentration following hemolytic Streptococcus respiratory disease.

Pattern Group III.—A third group was composed of 21 patients in whom a vigorous antibody response occurred, with peak antibody levels of 100 to 2500 units and a mean of 495 units per milliliter. This group showed a much more gradual fall than the second group, so that levels of less than 100 units per milliliter were not reached in 109 days in any case, and titers of this concentration or more were maintained for 197 or more days when information was available at appropriate intervals (13 cases). The essential data are presented in figure 2 and table 4. The cases in which the most adequate studies were available are included in the figure. The two groups are otherwise similar and may be considered together.

Respiratory infection, complicated by otitis media in four children, suppurative sinusitis in one and pyoderma in three, was present in all these children. Penicillin was never used for 12 of the children. Four received the drug early in the illness

and five after the peak of antibody response had occurred. The mean age of this group of children was 57.9 months. Only one was less than 18 months old, and only three were less than 40 months of age.

THE ROLE OF REINFECTION

The analysis just completed has demonstrated that well defined patterns of antistreptolysin response are observed following hemolytic Streptococcus infection in

TABLE 4.—*Essential Data in Seven Cases of Hemolytic Streptococcus Respiratory Infection in Which There Was a Gradual Decline in Antibody*

	Case No.						
	46	47	48	49	50	51	52
Age, Mo.	15	44	67	69	78	84	60
Peak antistreptolysin, units	166	500	333	2,500	166	333	500
on day	18	30	29	24	18	20	30
Lowest follow-up antistreptolysin value, units	100	166	166	500	125	250	166
on day	211	211	232	197	198	279	109
Penicillin therapy, day begun	18	14	None	None	2	None	None

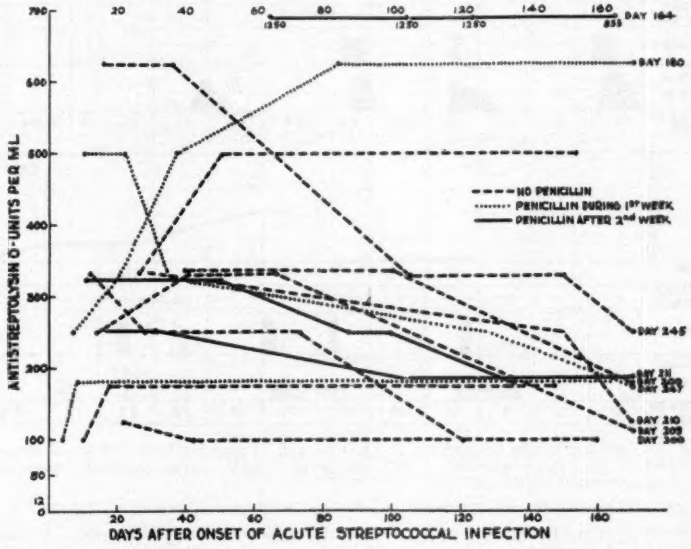

Fig. 2.—Graph showing pattern III antistreptolysin O response. This pattern is characterized by a well sustained serum antistreptolysin O level following hemolytic Streptococcus respiratory infection.

childhood. These variations in antibody phenomena are closely associated with the age of the subjects, and it is reasonable to suggest that the increased peak levels attained and the better maintenance of titers are simply the results of maturation of the antibody-forming apparatus.

Another hypothesis must be explored, that it is quite possible that similar changes in the nature of antibody response might occur as the result of conditioning

of the tissues of the growing child by repeated infection with hemolytic streptococci. The data obtained in six cases in which two or more group A hemolytic Streptococcus infections occurred in the first 30 months of life or less suggest that the latter mechanism may be of the greater importance. These cases will be briefly described and illustrated.

CASE 53 (top half, fig. 3).—A type 12 respiratory infection complicated by otitis media at the age of 15 months was treated late with penicillin. The associated antibody response was feeble and of pattern I. The patient was well and free of hemolytic streptococci until the twenty-first month, when a type 44 respiratory infection supervened. The illness was treated rather late with penicillin, and recovery was uneventful, but the antibody response was vigorous, a peak level of 625 units per milliliter being attained. A rapid fall in antibody was occurring during the twenty-third and twenty-fourth months, when a relapse or reinfection

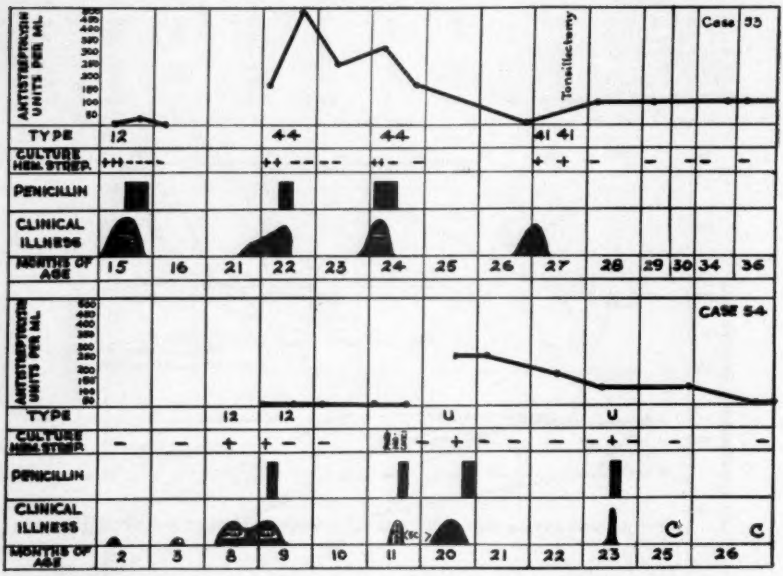

Fig. 3.—Antistreptolysin O response in cases 53 and 54 associated with multiple hemolytic Streptococcus respiratory infections. *U* indicates untypable strain; *OMAP*, otitis media purulenta acuta, and *C*, common cold.

by a strain of type 44 was discovered. A complicating otitis media was present. A standard course of treatment with penicillin was administered, and recovery was prompt. A slight increase in antistreptolysin may have occurred following this infection, but a rapid decline led to titers of only 12 units per milliliter 90 days after recovery from the third illness (pattern II). During the twenty-sixth month a fourth streptococcic infection caused by a strain of type 41 was detected. It was mild and was not treated with penicillin. Antistreptolysin was not produced as vigorously as after the second infection, perhaps because of the absence of a suppurative complication, but the level of 100 units per milliliter was exceedingly well maintained, having remained constant through the succeeding eight months (pattern III). This occurred in spite of tonsillectomy at 27 months, subsequent to which hemolytic streptococci were never again recovered from the nasopharynx.

CASE 54 (bottom half, fig. 3).—This child, who had been seen on several occasions previously because of nonstreptococcic respiratory disease, was first discovered to be suffering from a

respiratory infection with type 12 streptococci complicated by otitis media when she was 8 months of age. The process subsided without chemotherapy, but an exacerbation occurred, and penicillin administration was finally begun on the twenty-sixth day. Recovery was prompt and was not followed by the development of measurable antistreptolysin O during the subsequent two months (pattern I).

During her eleventh month pneumococcic otitis media was uneventfully controlled with penicillin therapy. A new streptococcic respiratory illness, caused by an untypable strain, was treated very late with penicillin and was followed by a pronounced increase in antistreptolysin. Two months later another infection by an untypable strain was treated early with penicillin, which apparently interrupted briefly a falling antibody level but failed to stimulate an increase. One month later a level of 12 units was reached (pattern II).

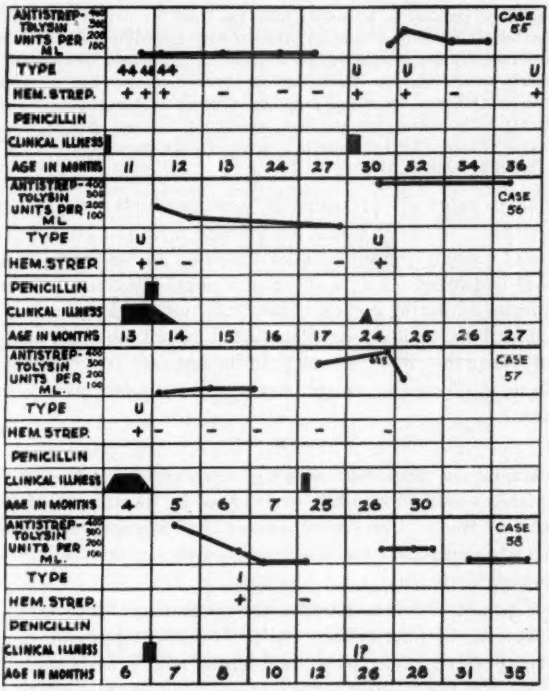

Fig. 4.—Antistreptolysin O response in cases 55, 56, 57 and 58 associated with reinfection by hemolytic streptococci.

CASE 55 (fig. 4).—A type 44 hemolytic Streptococcus respiratory infection was complicated by measles when this child was 11 months of age. Penicillin was not used. A maximum antistreptolysin titer of 12 units was attained and maintained through the twenty-seventh month (pattern I). In the thirtieth month another infection by an untypable strain was associated with a sharp increase in antibody to 250 units per milliliter. Four months later the titer was still 166 units per milliliter (pattern III).

CASE 56 (fig. 4).—This child was first seen during its thirteenth month on the fourteenth day of a respiratory infection caused by untypable hemolytic streptococci complicated by otitis media. Penicillin therapy was given in a standard course at this time. The maximum antistreptolysin titer was 166 units, and this fell to unmeasurable levels within four months

(pattern II). A subsequent mild infection by another untypable strain occurred during the twenty-fourth month. It was not treated with penicillin. The antibody response was vigorous, and a high antistreptolysin level of 500 units per milliliter was maintained without evidence of a decline for three months (pattern III).

CASE 57 (fig. 4.).—A prolonged illness caused by an untypable strain of hemolytic Streptococcus complicated by otitis media had been in progress for three weeks when this child was first seen at 4 months of age. No penicillin was given and spontaneous recovery occurred. Antistreptolysin levels of only 12 units per milliliter were reached during the succeeding two months (pattern I). Another illness appeared during the twenty-fifth month. When the child was first seen after this event, hemolytic streptococci had disappeared from the throat, but a vigorous and well maintained antistreptolysin response occurred (pattern III). No information is available concerning possible infections between the seventh and twenty-fifth months.

CASE 58 (fig. 4).—This case is somewhat different from the five just described in that a mild type 1 infection at 7 months of age, not treated with penicillin, was followed by a sharp increase in antistreptolysin and a rapid decline (pattern II). Another mild infection during the twenty-sixth month, which was not studied at an appropriate time for the recovery of the etiological agent, was followed by a less vigorous antibody response and a subsequent rapid decline (pattern II). The infant was not seen during the first six months, when a mild or inapparent infection followed by the pattern I response may have occurred. No history of such an illness could be elicited.

Comment.—Six cases are presented in which multiple infection by group A hemolytic streptococci occurred before the thirtieth month of life. In four an antibody response of pattern I was observed following the earliest infection and of either pattern II or pattern III after subsequent ones. All three patterns developed sequentially in case 52 during a cycle of four infections within the first 27 months. Pattern II followed the earliest infection studied (at 13 months), and pattern III the second (at 27 months) in a fifth case. In the last case (case 58) two infections, one at 6 and one at 26 months of age, were both associated with pattern II antibody responses.

COMMENT

The antistreptolysin response following hemolytic Streptococcus respiratory infection in infancy and childhood has been defined by the analysis of data obtained during a three year study. Cases were selected from a larger number for inclusion in the group to be considered for this report purely on the basis of adequacy of available information.

Three well defined patterns of antibody response were discovered. There was a surprising absence of intermediate types. No antistreptolysin, or exceedingly small amounts, appeared in the serum of a group with a mean age of 14 months (pattern I). Most of these patients were infants, although one was 4 years of age.

Suppurative complications, which were present in many of these cases, have usually been associated with vigorous production of antistreptolysin. The administration of penicillin [9] would not appear to be responsible for the blockade of antibody formation in these children, since several received the drug late or not at all. Furthermore, Lippard and Johnson [5] described a similar pattern in infants after streptococcic infection in 1935 before penicillin was available. Nor was this failure of antibody production an effect of the strain (or type) of Streptococcus causing the infection. The local types were distributed quite evenly throughout the pattern

9. Kilbourne and Loge.[3e] Weinstein, L.: Effect of Types of Treatment on Development of Antistreptolysin in Patients with Scarlet Fever, Proc. Soc. Exper. Biol. & Med. **63**:449, 1946.

groups. Furthermore, stimulation of antistreptolysin production by strains of various types has been shown previously to be constant.[10]

A second type of antibody response (pattern II) was observed in an older group of children whose age spread was without a sharp peak, from 11 to 76 months. The mean was 36.7 months. A moderate to sharp increment in antistreptolysin occurred in these cases, to be followed by a precipitous decline in serum antibody concentration so that low levels were attained in four months or less. The rapid falls in antibody were not related to the termination of the nasopharyngeal carrier state by penicillin administration or natural mechanisms.

Antibody production in the third group (pattern III) was vigorous, and levels were also well maintained, so that low titers (less than 100 units) were not reached after many months of observation. These children were older than those in whom the two previous patterns occurred, only two being less than 36 months of age. The mean age was 57.9 months.

An adequate explanation of these facts would be of considerable interest. Since, on the average, more vigorous antibody production and better sustained levels are associated with advancing age, it is tempting to assume that the infant is incapable of forming immune substances in large amounts because of some defect in the cellular mechanisms that is rectified by maturation. This point of view has been widely held in the past, but specific documentation of it is scanty except in the earlier reports of Park[11] dealing with diphtheria immunization. Three recent reports[12] are definitely contradictory and show clearly that even babies less than 6 months of age are capable of producing large amounts of diphtheria and tetanus antitoxin and influenza A and B hemagglutinins following immunization with toxoid in the usual amounts or with influenza virus vaccine. In none of these studies did older children form significantly larger amounts of any of these four antibodies.

It seems clear that the antibody-forming apparatus is fully capable of responding if the stimulus is adequate and that the variations of antibody pattern during childhood, which have been described in this report, cannot be regarded simply as the result of maturation. This is emphasized by the considerable overlapping of age groups exhibiting the three patterns.

The stimulus supplied by the initial infection with hemolytic streptococci must be regarded as inadequate. If so, an explanation for subsequent vigorous antibody production must be sought. It seems likely that this is the result of conditioning of the antibody-forming mechanism by repeated infection with hemolytic streptococci. Favoring this hypothesis are the well known investigations demonstrating that antibody production when partially immunized animals are restimulated is more vigorous than the initial response was. Unfortunately, no reference could be found to an experiment in which antigen injections, each alone too small to stimulate formation of antibody, would do so when administered sequentially.

10. Rantz, L. A.; Boisvert, P. J., and Clark, W. H.: The Relationship of Serological Types of Group A to Toxin Formation and Antibody Response, Stanford M. Bull. **6**:55, 1948.

11. Park, W. H.: Toxin-Antitoxin Immunization Against Diphtheria, J. A. M. A. **79**:1584 (Nov. 4) 1922.

12. Cooke, J. V.; Hollowach, J.; Atkins, J. E., and Powers, J. R.: Antibody Formation in Early Infancy Against Diphtheria and Tetanus Toxoids, J. Pediat. **33**:141, 1948. Peterman, M. G., and Kores, V.: Influenzal Vaccination in Infants and Children, Pediatrics **4**:337, 1949. Quilligan, J. J.; Minure, E., and Francis, T.: Homologous and Heterologous Antibody Response of Infants and Children to Multiple Injections of a Single Strain of Influenza Virus, J. Clin. Investigation **27**:572, 1948.

The data obtained from the study of six infants presented in this report in whom reinfection by new strains of group A streptococci occurred within the first 30 months of life favor this proposed mechanism. In five instances the antibody response after the second infection was different and of a more mature type than that following the first, even though the multiple infections succeeded one another in time quite closely. In one case all three immunologic patterns were observed in numerical sequence following four infections before the child was 28 months old.

The possible relationship of these immunologic phenomena, probably the result of alteration in the antibody-forming functions as the result of reinfection by hemolytic streptococci, to the natural history of streptococcic disease and the pathogenesis of the nonsuppurative complications, such as rheumatic fever, is of great importance.

Powers and Boisvert [4] have described the change in the nature of hemolytic Streptococcus respiratory infection with increasing age of children. They have noted that an indolent low grade process, often associated with suppurative complications, which is commonly observed in the first two years of life is replaced by a much more acute, short-lived disease usually not accompanied with suppurative complications. Furthermore, they have pointed out that a skin rash is not usually seen early in childhood and that rheumatic fever is a rare sequel before the fifth year of life. These investigators have postulated that the alterations in the natural history of streptococcic disease are the result of reinfection by hemolytic streptococci, which is thought to lead to sensitization of the tissues and altered response to subsequent infection. Such sensitization would be presumably an immunologic phenomenon. The results of the study reported here are in accord with this hypothesis and lend some support to it in that a changing immunologic pattern with advancing age presumably caused by reinfection has been discovered.

These observations also make a contribution to the elucidation of the pathogenesis of rheumatic fever. Previous work based on clinical and bacteriologic study [3a] and on animal investigation [13] has strongly suggested that rheumatic fever results from repeated infection by group A hemolytic streptococci leading, in all probability, to sensitization and tissue damage by an immunologic reaction.

Previous immunologic investigation [14] has established certain facts in regard to the mechanics of the antistreptolysin response when group A hemolytic Streptococcus infection is followed by the development of rheumatic fever. The production of antibody is vigorous, the substance being formed on the average in greater amounts than in uncomplicated cases, and the levels are well maintained. We are unaware, either from an examination of published information or from an extensive personal experience, of definite rheumatic fever in children or adults who exhibited antibody patterns I or II, as described in this report. Cases are seen in which titers of antistreptolysin in the range of 100 units per milliliter are present, but even here rapid falls to low levels are excessively rare. In a few cases in our experience in which low titers of antibody were present throughout (possibly pattern I), subsequent study revealed that another of the diffuse collagenous diseases was present.

13. Murphy, G. E., and Swift, H. F.: Induction of Cardiac Lesions, Closely Resembling Those of Rheumatic Fever, in Rabbits Following Repeated Skin Infections with Group A Streptococci, J. Exper. Med. **89**:687, 1949.

14. Footnotes 2 and 3.

None of the children considered in this report acquired frank rheumatic fever. Those exhibiting antibody patterns I or II recovered promptly after the acute suppurative process was controlled. There was a rapid fall of the erythrocyte sedimentation rate, and the electrocardiogram was normal throughout. Recovery was slower in approximately 15 per cent of those in whom pattern III was discovered; the erythrocyte sedimentation rate was rapid for long periods, and minor electrocardiographic changes were observed. These clinical observations will be the subject of future reports.

The available information, including that contained herein, indicates that rheumatic fever is a sequel to hemolytic Streptococcus infection in persons whose antistreptolysin response is of a certain type (pattern III). There is considerable reason to believe that this antibody pattern is the result of serial reinfection of the person by group A streptococci. Thus, some additional support is given to the hypothesis that reinfection by these organisms is essential for the development of the rheumatic state.[15] Obviously other unknown factors are at work, since in many persons infected by hemolytic streptococci and exhibiting an antistreptolysin response of pattern III a nonsuppurative complication fails to develop. The fact that the development of rheumatic fever is associated with a poststreptococcic antibody pattern different from that seen in certain human beings who, following infection, do not suffer from this disorder may also add some weight to the theory that an essential immunologic process is involved in the pathogenesis of the disease. Streptolysin O and its antibody probably have no direct role in this process but may well offer a measurable index to some aspects of streptococcic antibody mechanics in human beings.

SUMMARY

Respiratory infection with group A hemolytic Streptococcus and the associated antistreptolysin response were studied in infants and children. Three distinct antistreptolysin response patterns were discovered. Antibody production was feeble in infants and a few older children. The response was vigorous, but levels of antibody were poorly maintained in a group with an older average, but with wide extremes of, age. The response was vigorous and titers were well maintained in a still older group of children.

Evidence is presented which indicates that these varying patterns of antibody response with advancing age are the result of conditioning of the antibody-forming organs by repeated infection with hemolytic streptococci rather than of maturation of these tissues.

The possible relationship of the immunologic phenomena in the elucidation of the pathogenesis of rheumatic fever is discussed.

15. Murphy and Swift [13] presented immunologic data obtained from three of their rabbits that displayed an experimental disease similar to rheumatic fever after serial dermal group A Streptococcus infections. The antistreptolysin O response was feeble in the first two through cycles of seven and four infections, respectively. With the onset of the nonsuppurative disorder there was a striking production of antibody. The third rabbit was somewhat similar except that certain of the earlier infections were associated with an evanescent antibody response similar to pattern II of this report, and the increment of antibody at the time of the appearance of the rheumatic-fever-like process was not so vigorous. The immunologic events in these rabbits were similar to those described in infants and children in this report.

MULTILOBAR PULMONARY VENOUS OBSTRUCTION WITH PULMONARY HYPERTENSION

"Protective" Arterial Lesions in the Involved Lobes

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IN THE presence of structural obstruction to the free flow of blood from the lungs to the left ventricle, such as in classic mitral stenosis, proliferative thickening of the walls of the small arteries and arterioles occurs.[1] It has been conjectural whether such changes are coincidental findings related to high pressures in the left atrium and pulmonary artery or whether, in some unique way, they cause pulmonary hypertension in excess of the obstruction to venous outflow and at times protect the pulmonary capillaries against excessive pressures. The absence of correlation between increased pulmonary arterial pressures and clinical evidence of pulmonary congestion in patients having mitral stenosis led Borden and associates [2] to conclude that, in addition to the reflected high pressures in the left atrium, an anatomic obstructive factor existed in the pulmonary vascular tree. The absence of increased volume of pulmonary blood among patients with mitral stenosis, as reported by Borden and co-workers [3] and Lagerlöf and associates,[4] is consistent with this hypothesis. Furthermore, for patients having congenital cardiac malformations in which the right ventricle assumes the role of a systemic ventricle, the thickened small pulmonary arteries have real functional significance in preventing excessive pulmonary flow.[5]

Dr. Edwards is from the Section on Pathologic Anatomy and Dr. Burchell from the Division of Medicine, Mayo Clinic.

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3. Borden, C. W.; Ebert, R. V.; Wilson, R. H., and Wells, H. S.: Studies of the Pulmonary Circulation: II. The Circulation Time from the Pulmonary Artery to the Femoral Artery and the Quantity of Blood in the Lungs in Patients with Mitral Stenosis and in Patients with Left Ventricular Failure, J. Clin. Investigation **28**:1138-1143 (Sept.) 1949.

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The case reported herein is one of acquired pulmonary venous obstruction in which the pulmonary veins were constricted unequally. Decided arterial and arteriolar changes were present in the lobes with severe pulmonary venous obstruction, and minimal changes were evident in the vessels of the lobe with only mild pulmonary venous obstruction. In the latter lobe evidence of marked "vascular congestion" was seen in the roentgenogram of the thorax; the rest of the lung fields failed to show evidence of congestion by this method of examination. The central pulmonary arterial pressure was moderately elevated. In the lobes in which venous outflow was obstructed, it appeared that the vascular changes prevented capillary engorgement.

REPORT OF A CASE

A married woman, 26 years of age, was well until January 1944, when cough and night sweats developed and loss of weight became progressively severe. She was admitted to a sanatorium where she remained for eight months; her symptoms gradually disappeared. She never raised any sputum, and results of tuberculin tests were negative. In August 1948 the nonproductive cough recurred and was associated with dyspnea which increased on slightest exertion. Two months later she suffered from orthopnea and increasingly severe paroxysms of dyspnea. These symptoms were present when she was admitted to the Mayo Clinic on Oct. 27, 1948 and was hospitalized. A faint apical systolic murmur was noted associated with an accentuated first sound at the apex and a loud second sound in the pulmonary area. A few rales were heard at the base of the right lung. A roentgenogram of the thorax showed a cardiac silhouette consistent with that of mitral stenosis and evidence of congestion localized in the lower field of the right lung (fig. 1). Mitral stenosis was the initial provisional diagnosis, although auscultatory and roentgenoscopic findings did not support such a diagnosis. The electrocardiogram showed low amplitude of the QRS complexes and flat T waves in the extremity and precordial leads. It was noncontributory to the diagnosis. An R wave of 0.4 millivolt was present in V_1 in relation to an S wave of 1.2 millivolts. The systemic blood pressure was 122 mm. of mercury systolic and 82 diastolic.

In the hospital the patient continued to have episodes of severe coughing, severe dyspnea and weakness. A left atrial tumor was considered as a diagnostic possibility. Diagnostic catheterization of the heart was believed indicated particularly to evaluate the degree of pulmonary hypertension, and this was carried out in the laboratory of Dr. E. H. Wood. The systolic and diastolic pressures recorded in the right pulmonary artery, pulmonary trunk and right ventricle were 90 and 45, 98 and 45 and 96 and 10 mm. of mercury. The cardiac output was 3.2 liters per minute, and the cardiac index was 2.1 liters per minute per square meter. The patient died during a paroxysm of dyspnea several hours after catheterization.

Pathological Features.—At postmortem examination pertinent findings were limited to the heart, lungs, posterior mediastinum and pulmonary veins. In the posterior mediastinum inferior to the bifurcation of the trachea and centered somewhat to the left of the midline a large gray firm mass, the consistency of cartilage, presented itself (fig. 2). Within the mass was a spherical lesion measuring 1 cm. in diameter. It was yellowish gray and soft and resembled a caseous lymph node. Microscopically the large mass was composed of dense bundles of relatively acellular collagen with no cellular reaction. The mass measured 7 cm. from above downward, 4 cm. from side to side and 2.5 cm. from before backward. It lay primarily in the posterior mediastinum and also involved the adjacent portion of the posterior parietal pericardium. In its

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H. B., and Christensen, N. A.: Pathology of the Intrapulmonary Arteries and Arterioles in Coarctation of the Aorta Associated with Patent Ductus Arteriosus, Am. Heart J. **38**:205-233 (Aug.) 1949. (*c*) Dexter, L.; Dow, J. W.; Haynes, F. W.; Whittenberger, J. L.; Ferris, B. G.; Goodale, W. T., and Hellems, H. E.: Studies of the Pulmonary Circulation in Man at Rest: Normal Variations and the Interrelations Between Increased Pulmonary Blood Flow, Elevated Pulmonary Arterial Pressure, and High Pulmonary "Capillary" Pressures, J. Clin. Investigation **29**:602-613 (May) 1950. (*d*) Edwards, J. E.: Structural Changes of the Pulmonary Vascular Bed and Their Functional Significance in Congenital Cardiac Disease, Proc. Inst. Med. Chicago **18**:134 (June 15) 1950.

pericardiac location the mass involved the pulmonary veins. On the left side the superior and inferior pulmonary veins joined to form a common trunk which, in turn, entered the left atrium. This common left pulmonary vein was constricted by the mediastinal mass to the extent that

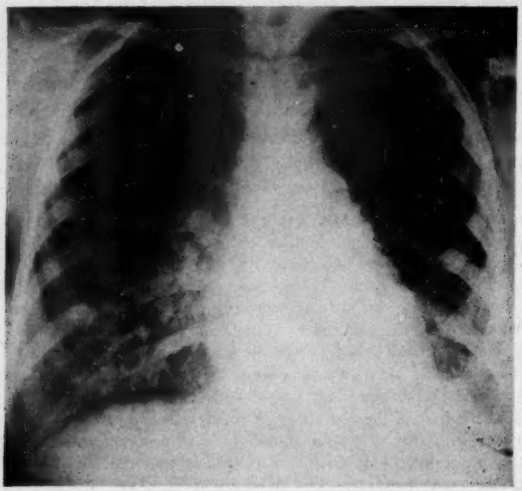

Fig. 1.—Note the prominence of the shadow of the pulmonary trunk and evidence of congestion in the lower field of the right lung.

Fig. 2.—Posterior view of bifurcation of the trachea. Inferior to the bifurcation is the mass which involved the posterior mediastinum. Although suggested by the illustration, the left main bronchus is not narrowed.

the vein admitted only a fine probe (fig. 3). At its narrowest zone the vein measured less than 2 mm. in diameter. On the right side the veins of the upper and middle lobes joined to

form a right superior pulmonary vein which, in turn, entered the left atrium. The inferior lobe of the right lung was drained by the right inferior pulmonary vein, which likewise entered the left atrium. The mass compressed the right superior pulmonary vein and its two tributaries so that the lumen of each of these veins measured about 1 mm. in diameter. The right inferior pulmonary vein was only moderately compressed. At its narrowest point the lumen of this vein measured 6 mm. in diameter. The right inferior pulmonary vein seemed thus the only effective channel leading from the lungs to the left atrium. The heart showed moderate dilatation and hypertrophy of the right ventricle. The wall of the right ventricle measured 0.5 to 0.7 cm. in thickness; that of the left ventricle, 1.1 cm. The foramen ovale was anatomically closed. The valves and coronary vessels were normal. The ductus arteriosus was closed. Cardiac lesions as a result of the catheterization were not found.

The major pulmonary arteries were moderately thickened and gray. Atheromas were not present. The pulmonary lobes presented two contrasting appearances; the lower lobe of the right lung represented one and the remaining lobes represented the other appearance. The lower lobe of the right lung may hereinafter be referred to as the "unobstructed" lobe, while the upper and middle lobes of the right lung and the two lobes of the left lung will collectively be called the "obstructed" lobes.

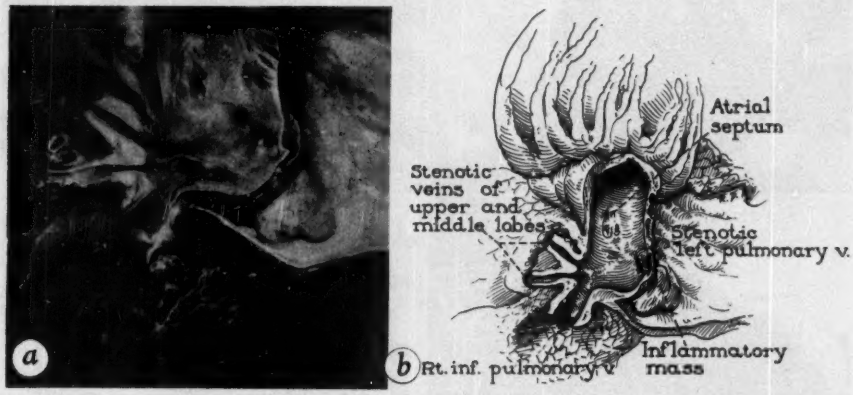

Fig. 3.—(*a* and *b*) Superoposterior wall of left atrium from the front showing severe stenosis of the left pulmonary vein and of pulmonary veins from the upper and middle lobes of the right lung. The right inferior pulmonary vein is only mildly constricted. (*b*) The heart is shown reflected upward after the lower posterior wall of the left atrium has been cut.

The lower lobe of the right lung was distended, purple and subcrepitant. When cut, a great amount of frothy blood-stained nonviscid fluid flowed from the moist grayish red surface.

The unobstructed lobes were pale. Their cut surfaces were pale and dry. The visceral pleura covering these lobes showed prominent tortuous vessels containing bright red blood. Several vascular fibrous adhesions bound the left lung to the adjacent parietal pleura. Scattered through the lungs were a few spherical, partly calcified, partly caseous nodules measuring up to 0.6 cm. in diameter.

A striking dissimilarity was noted in the microscopic appearance of the blood vessels in the lower lobe of the right lung as compared with that of the vessels in all the other pulmonary lobes (fig. 4). In the lobes in which serious obstruction to venous flow existed, severe occlusive lesions involved the arterioles and the smaller arteries. Changes in these categories of blood vessels in the lower lobe of the right lung, on the contrary, were minimal, and the structures deviated only little from the normal.

The small arteries of the obstructed lobes revealed two morphological changes; namely, medial muscular hypertrophy and intimal fibrous thickening, each of which caused significant luminal narrowing. Frequently the two changes coexisted. At times the walls were greatly

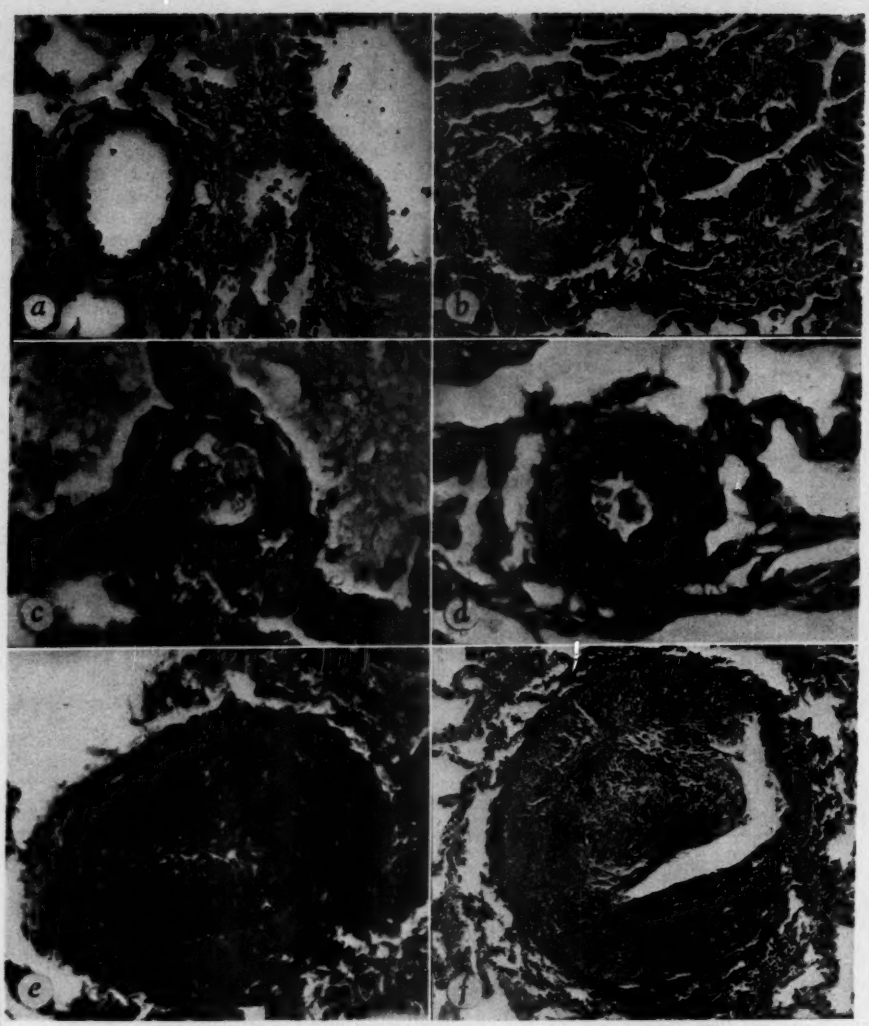

Fig. 4.—(*a*) In the lower lobe of the right lung a muscular artery has an essentially normal structure. Contrast with *b*. Masson trichrome stain; ×130. (*b*) In the lower lobe of the left lung a muscular artery shows pronounced medial hypertrophy and intimal fibrous thickening causing severe luminal narrowing. Masson trichrome stain; ×130. (*c*) An arteriole in the lower lobe of the right lung has an essentially normal structure. The alveolar walls are congested. Contrast with *d*. Verhoeff's elastic tissue stain counterstained with Van Gieson's connective tissue stain; ×400. (*d*) Arteriole from the lower lobe of the left lung showing pronounced fibrous thickening of the wall causing significant luminal narrowing. Verhoeff's elastic tissue stain counterstained with Van Gieson's connective tissue stain; ×435. (*e*) Small muscular artery from the upper lobe of the left lung showing medial hypertrophy and severe intimal fibrosis. The latter results in almost complete closure of the lumen. Verhoeff's elastic tissue stain counterstained with Van Gieson's connective tissue stain; ×400. (*f*) A thin-walled vessel, presumably a vein, in the upper lobe of the left lung, shows pronounced intimal fibrous thickening with corresponding luminal narrowing. Verhoeff's elastic tissue stain counterstained with Van Gieson's connective tissue stain; ×95.

thickened by cells and collagen, the cells resembling fibroblasts, and it was impossible to distinguish between the intima and the media. The arterioles showed fibrous thickening. Some vessels had little media and tremendous fibrous nonintimal thickening which caused almost complete obliteration of the lumen. While these vessels could have been dilated arteries, they were possibly pulmonary venous tributaries.

As a rule, the arterioles and small arteries in the lower lobe of the right lung, that is, the unobstructed lobe, were normal, in striking contrast to those in the other lobes. Rare arteries displayed mediae which could be interpreted as showing borderline degrees of medial hypertrophy. A rare vessel showed a mild degree of intimal fibrous thickening, but in none was this change sufficient to produce any appreciable degree of luminal narrowing.

The lower lobe of the right lung was the site of considerable alveolar capillary engorgement and many intra-alveolar macrophages containing hemosiderin. In the obstructed lobes there were moderate numbers of alveolar macrophages, the majority of which were nonpigmented. The obstructed lobes were not congested. In all lobes many of the alveolar walls contained abundant elastic fibers, and in the obstructed lobes there were foci in which the alveolar walls were thickened by collagen. In such areas the lining epithelial cells were recognizable as simple cuboidal epithelium.

COMMENT

The mass which involved the posterior mediastinum and the pulmonary veins is considered to be of inflammatory origin. With evidence of a healed pulmonary granulomatous disease, we are of the opinion that at some time in the past a posterior mediastinitis had existed and that in the healing process there was a keloid-like reaction which resulted in the dense collagenous mass.

Owing to the severe degree of pulmonary venous stenosis, we are of the opinion that little blood circulated through the left lung and through the upper and middle lobes of the right lung. The burden of the flow of pulmonary blood fell on a single lobe, the lower lobe of the right lung, which is interesting in view of the central pulmonary hypertension that had been demonstrated by cardiac catheterization. It is known from reported studies on human beings that when one lung is removed pulmonary hypertension does not result if the remaining lung is normal,[6] although some hypertension may be demonstrated[6a] with increased flow due to exercise. The ability of the pulmonary vascular bed to accommodate to increased volumes of blood without elevation of pulmonary blood pressure also is demonstrated in many cases of atrial septal defect, ventricular septal defect, patent ductus arteriosus and partial anomalous drainage of the pulmonary veins. It is well established that the lungs may accommodate to volumes of blood much greater than normal without development of pulmonary hypertension. Nevertheless, a limit to this capacity of accommodation to increased flow without greatly increased pressure does exist. In the case which we are describing, pulmonary hypertension existed when most of a normal volume of pulmonary blood flowed through the vascular bed of one lobe. In this lobe vascular changes were not significant.

Our observations indicate that one lobe of a lung, even with essentially normal vessels, is incapable of carrying a normal flow of pulmonary blood without causing a state of pulmonary hypertension. Thus, it would seem that with normal pulmonary vessels the vascular bed necessary for accommodation of normal volumes

6. (*a*) Cournand, A.; Riley, R. L.; Himmelstein, A., and Austrian, R.: Pulmonary Circulation and Alveolar Ventilation-Perfusion Relationships After Pneumonectomy, J. Thoracic Surg. **19**:80-116 (Jan.) 1950. (*b*) Zimmerman, H. A.; Mendelsohn, H., and Adelman, A.: A Study of Pulmonary Hemodynamics During Pneumonectomy: A Preliminary Report, J. Lab. & Clin. Med. **34**:1769-1770 (Dec. pt. 2) 1949.

of pulmonary blood must lie between that of one lobe of a lung and that of one lung. This observation is consistent with that of Dexter and associates,[5c] who demonstrated that in the presence of normal lungs a fourfold increase in flow of pulmonary blood must exist for the central pulmonary arterial pressure to become elevated.

Completely adequate clinical or roentgenologic data are not available on which to base statements, with certainty, to the effect that the pulmonary edema which occurred during the episodes of acute dyspnea was limited to the lower lobe of the right lung; however, this is considered probable. The lobes of the lungs with severe obstruction to the pulmonary venous outflow had pronounced arteriolar and small arterial lesions, and it seems reasonable to suppose that the narrowing of these vessels protected the pulmonary capillaries from excessive pressures and volumes of blood.

It should be pointed out that the pulmonary arteriovenous pressure gradient was different in the lobes with marked pulmonary venous obstruction from that in the lobe without much obstruction and that the mean pressures would be higher in the arteriolar bed of the obstructed lobes.

SUMMARY

A woman, 26 years of age, had severe acquired venous stenosis in all except one pulmonary lobe. Cardiac catheterization demonstrated central pulmonary hypertension and a normal volume of pulmonary blood flow. The lobe without significant venous stenosis had essentially normal arterioles and small arteries; in the remaining lobes there were severe occlusive vascular changes similar to those seen in some cases of mitral stenosis. Severe pulmonary congestion was present in the lobe without venous obstruction, but congestion was not present in the other lobes. It is postulated that the occlusive arterial and arteriolar lesions in the lobes with severe venous obstruction protected the pulmonary capillaries from excessive passive congestion and from elevations of pressure.

Since most of the pulmonary blood flowed through the one essentially normal lobe, the existing central pulmonary hypertension is explained as follows: The capacity of the blood vessels in one normal pulmonary lobe is inadequate to carry the entire, although normal, volume of pulmonary blood flow without elevation of pressure.

INTERMITTENT PERITONEAL LAVAGE IN NEPHRECTOMIZED DOGS AND ITS APPLICATION TO THE HUMAN BEING

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With the Technical Assistance of Maurine Giese, William M. Ott and Gordon M. Gafford
DALLAS, TEXAS

PREVIOUS studies on the use of artificial measures (the artificial kidney, exchange blood transfusions, peritoneal lavage, etc.) to maintain life in the absence of renal function have been carried out chiefly on the human patient. Thus, a total of 101 patients have been treated by continuous peritoneal lavage,[1] but the value of the method remains equivocal because many patients with acute anuria recover spontaneously when treated by more conservative measures.[2] It was deemed necessary, therefore, to carry out studies on the nephrectomized animal in order to establish the potentialities of the method before proceeding to its application to the human patient.

The present paper describes procedures for performing peritoneal lavage, by means of which it has been possible to maintain bilaterally nephrectomized dogs for periods of 30 to 70 days, which is several times that ever reported previously. With consideration of the inevitable malignant hypertension that develops following nephrectomy,[3] the survival period attained may be regarded as evidence of an adequate replacement for the excretory function of the kidneys. We have also applied the procedure to five human patients with acute anuria to demonstrate the applicability of our simplified procedure to the clinic. As shown later, we feel that the method not only is the best available for experimental purposes in the laboratory but also has many advantages over the use of the artificial kidney or exchange transfusion, the other methods now employed clinically.

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Dr. Grollman is Professor of Experimental Medicine, Southwestern Medical School of the University of Texas, and Attending Physician, Parkland Hospital. Dr. Turner is Fellow of the Dazian Foundation for Medical Research. Dr. McLean is Research Fellow in Experimental Medicine.

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2. Muirhead, E. E.; Vanatta, J., and Grollman, A.: Acute Renal Insufficiency: A Comparison of the Use of an Artificial Kidney, Peritoneal Lavage and More Conservative Measures in Its Management, Arch. Int. Med. **83**:528 (May) 1949.

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The present investigation is an extension of earlier studies on procedures for maintaining the life of nephrectomized dogs. The usual survival of such animals when untreated is only 48 to 120 hours under optimal conditions. By restricting the animal's diet to a salt-free, low protein mixture, survival may be extended to an average of about five days. By the use of an artificial kidney or exchange transfusions, this period of survival was further extended to a maximum of 19 days with an average of about 10 days.[4] Seligman, Frank and Fine[5] reported survival periods of 6, 9 and 13 days in three dogs subjected to continuous peritoneal irrigation. Abbott and Shea[6] succeeded in maintaining three nephrectomized dogs alive for seven, eight and nine days, respectively, by their technic of peritoneal lavage. The longest survivals hitherto reported using peritoneal lavage are those of Bliss, Kastler and Nadler,[7] who maintained two dogs for 13 and 16 days. With the exception of the cited work from this laboratory,[8] the application of the artificial kidney to the dog has met with no success.

The peritoneum has long been recognized as an excellent dialyzing membrane with a filtering surface (approximately 22,000 square centimeters) comparable to that of the renal glomeruli.[1] Earlier workers demonstrated the shifts of water and solutes across the peritoneal membrane in either direction, depending on the relative concentrations of various constituents in the blood and peritoneal cavity. By the use of hypotonic solutions, it is possible to cause a shift of extracellular water into the cells with the development of overhydration; contrariwise, hypertonic solutions produce a shift of water from the cells to the extracellular compartment with the induction of dehydration. By altering the composition of the bathing fluid, it is, therefore, possible to alter the composition as well as the volume of the tissue fluids.

MATERIALS AND METHODS

Adult mongrel dogs of either sex, weighing between 7 and 12 Kg., were nephrectomized bilaterally in one or two stages by the technic previously described.[3] For extended survival, introduction of fluid into and its removal from the peritoneal cavity need be performed only twice daily with an interval of at least three hours between the two manipulations. As will be shown later, the blood level of urea and other catabolic waste products remains relatively high under these conditions, but the normal water and electrolyte balance is maintained, and the animal remains in relatively good condition, as shown in figure 1. However, one can reduce the level of the nitrogenous constituents of the blood to relatively normal values by repeating the lavage every 1.5 to three hours.

At various times following nephrectomy, blood samples were removed for analysis by puncture of the femoral artery. The following procedures were used: Plasma sodium was determined gravimetrically by the modified Butler-Tuthill procedure[9]; plasma chloride, by the colorimetric

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6. Abbott, W. E., and Shea, P.: The Treatment of Temporary Renal Insufficiency by Peritoneal Lavage, Am. J. M. Sc. **211**:312, 1946.

7. Bliss, S.; Kastler, A. O., and Nadler, S. B.: Peritoneal Lavage: Effective Elimination of the Nitrogenous Waste in the Absence of Kidney Function, Proc. Soc. Exper. Biol. & Med. **29**:1078, 1932.

8. Grollman and others.[3] Vanatta and others.[4]

9. Butler, A. M., and Tuthill, E.: An Application of the Uranyl Zinc Acetate Method for Determination of Sodium in Biological Material, J. Biol. Chem. **93**:171, 1931.

method of Stiff [10]; plasma carbon dioxide-combining power, by the direct method of Van Slyke and Cullen [11]; plasma potassium by the photoelectrometric procedure of Looney and Dyer [12]; serum calcium by the method of Clark and Collip [13]; serum magnesium by the method of Hawk, Oser and Summerson [14]; plasma urea, by Summerson's modification of Van Slyke and Cullen's procedure [14]; plasma nonprotein nitrogen and creatinine, by the colorimetric methods of Folin and Wu [15]; inorganic phosphate, by the method of Fiske and SubbaRow [16]; inorganic sulfate, by the colorimetric method of Letonoff and Reinhold,[17] and phenols, by the method of Theis and Benedict.[18]

Composition of Irrigation Fluid.—The composition of the irrigating fluid necessary for maintaining normal blood levels was determined empirically by following the blood chemical values with variations in composition of the irrigating fluid. The ionic composition of the basic formula thus arrived at is shown in table 1. To each liter of this solution were added 25,000 units of sodium penicillin and 25 mg. of streptomycin. By the use of these antibiotics and the maintenance of the usual aseptic technic in making the peritoneal injections, infection was prevented both in the animal and in the human subjects. In the latter, however, the intramuscular injection of 300,000 units of aqueous procaine penicillin daily, which the patients were receiving prior to the lavage, was continued as an extra precautionary measure against infections. It has not been found necessary to add heparin to the perfusing fluid as advocated by earlier workers. However,

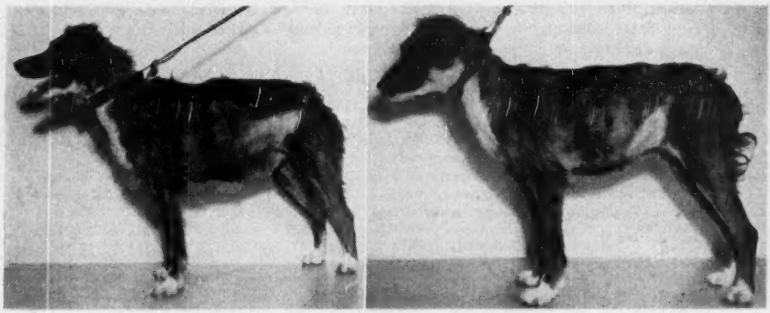

Fig. 1.—The appearance of dog 19 prior to nephrectomy (left) and 30 days later (right) while maintained by intermittent peritoneal lavage.

the dosage of streptomycin used may prove toxic when multiple irrigations are performed daily on the dog and must, therefore, be reduced under these conditions.

10. Stiff, H. A.: The Colorimetric Determination of Blood Chloride by the Iodometric Method, J. Biol. Chem. **172**:695, 1948.

11. Van Slyke, D. D., and Cullen, G. E.: Studies of Acidosis: I. The Bicarbonate Concentration of the Blood Plasma; Its Significance, and Its Determination as a Measure of Acidosis, J. Biol. Chem. **30**:289, 1917.

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13. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification, J. Biol. Chem. **63**:461, 1925.

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16 Fiske, C. H., and SubbaRow, J.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375, 1925.

17. Letonoff, T. V., and Reinhold, J. G.: A Colorimetric Method for the Determination of Inorganic Sulfate in Serum and Urine, J. Biol. Chem. **114**:147, 1936.

18. Theis, R. C., and Benedict, S. R.: The Determination of Phenols in the Blood, J. Biol. Chem. **61**:67, 1924.

The ionic composition of the perfusion fluid as given in table 1 was suitable for maintaining dogs for prolonged periods by two lavages daily. However, its composition must be varied when multiple lavages are performed. Under these conditions it is necessary to increase the amounts of calcium chloride, magnesium chloride and potassium chloride to 0.25 Gm., 0.1 Gm. and 0.4 Gm. per liter, respectively, in order to maintain a normal blood electrolyte level if the animal is maintained on the electrolyte-free diet described later. On the other hand, in patients with an initially high blood potassium level the potassium chloride is omitted entirely.

In order to delay the rate of absorption of the peritoneal fluid, it is necessary to make it hypertonic by the addition of dextrose in amounts varying from 0.1 to 7 per cent. The effect of variation in dextrose content and the factors determining the amount used under given conditions are discussed later.

Triple distilled pyrogen-free water was used in preparing the solutions. In the case of solutions for administration to the human subjects, the isotonic sodium chloride solution U. S. P., 10 per cent dextrose solution in water and 50 per cent dextrose solution in water generally available for intravenous injection were used in amounts necessary to prepare the desired solution. To this was added the necessary amount of the other constituents.

The composition of the fluid described in table 1 differs in several respects from that advocated by Fine, Frank and Seligman [19] and other earlier workers in the field. In view of the tendency for phosphate to be increased in anuria, it was deemed unnecessary, for example, to add this ion to the solution. Even with its absence from the perfusion fluid, the inorganic phosphate content of the plasma tends to be high in the nephrectomized animal or anuric patient.

TABLE 1.—*Electrolyte Content of Perfusion Fluid*

	Gm./L.	$[Na^+]$	$[Cl^-]$ mEq./L.	$[HCO_3^- — CO_3^=]$
NaCl	5.77	98.7	98.7	....
$CaCl_2$	0.20	....	3.6	....
$MgCl_2$	0.05	....	1.1	....
KCl	0.20	....	2.7	....
$NaHCO_3$	3.00	35.8	....	35.8
Total	....	134.5	106.1	35.8

Diet.—The nephrectomized dogs were fed a synthetic diet administered by stomach tube two or three times daily. By this means it was possible to insure an adequate dietary intake, which is otherwise difficult in view of the poor appetite in uremia, as well as in malignant hypertension. The use of a synthetic diet also permits one to control the composition of the diet so as to avoid an excess of inorganic salts and protein. The diet which we have used is a modification of that of Bull, Joekes and Lowe [20] and has the composition shown in table 2. Its purpose is to supply adequate calories by the use of fat and carbohydrate, the necessary minimal protein content to reduce tissue catabolism to a minimum and the known essential vitamins. The polysorbate 80 is added in order to emulsify the mixture. This synthetic diet has also been found of value in treatment of patients with acute anuria or other forms of renal excretory failure.

The amount of the diet fed was proportional to the size of the dog and was calculated to furnish approximately 70 calories per kilogram of body weight. Each liter of the diet mixture has a value of approximately 2,230 calories.

Procedure.—In the dog, a 17 gage needle, 9 cm. long, was inserted into the peritoneal cavity through the flank. The irrigating fluid, brought to body temperature, was introduced by gravity through this needle from a suspended bottle as in the ordinary intravenous infusion. The fluid was allowed to remain in the peritoneum for varying periods and then siphoned off through the same sized needle connected by an adapter to a rubber tube. Drainage required about 30 minutes

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20. Bull, G. M.; Joekes, A. M., and Lowe, K. G.: Conservative Treatment of Anuric Uraemia, Lancet **2**:229, 1949.

and was followed by refilling, which required only about five minutes. This procedure was carried out twice daily, usually in the morning and late afternoon. Although more frequent exchange permits a further reduction in the level of the urea and other catabolites, this is unnecessary so far as survival of the dog is concerned.

Application of Procedure to the Human Being.—The procedure of peritoneal lavage as elaborated for the dog has been applied to the human subject with certain necessary alterations. The solution of table 1 (modified as described later depending on the status of the patient and the end result to be attained so far as water and the electrolyte pattern are concerned) and intermittent lavage at two hour intervals were employed. The fluid was introduced and drained through a single opening in the anterior abdominal wall. A trocar was inserted as in the routine removal of ascites fluid, the stylet replaced with a polyethylene plastic tube and the trocar removed. The plastic tube, to which omentum does not attach itself, was allowed to remain throughout the procedure, being connected alternately through a needle to an adapter and rubber drainage tube and to the infusion bottle. This simple procedure proved adequate and avoided the complex apparatus used in continuous irrigation by previous investigators.

Blood Transfusion.—The tendency to develop anemia in uremia is well known in the human being. The degree of anemia is, in general, proportional to the level of the azotemia and is in part a result of a hemolytic tendency and in part due to failure of erythropoiesis. In the nephrectomized dog sustained for prolonged periods by artificial measures, anemia of a severe degree

TABLE 2.—*Constituents Used in Preparing 2,600 Cc. of a Salt-Free Diet*

Water	1,500 cc.	Pantothenic acid	5 mg.
Peanut oil	420 cc.	Nicotinamide	5 mg.
Lactalbumin	200 Gm.	Inositol	50 mg.
Dextrose (or sucrose)	500 Gm.	Paraaminobenzoic acid	50 mg.
Ferrous sulfate	2 Gm.	2-methyl, 1-4 napthoquinone	1 mg.
Liver concentrate	1 Gm.	Ascorbic acid	2,000 mg.
Vitamin A *	5,000 U. S. P. units	Rice bran concentrate	500 mg.
Vitamin D	500 U. S. P. units	Linoleic acid	500 mg.
Thiamine hydrochloride	6 mg.	Tocopherol	50 mg.
Riboflavin	6 mg.	Choline chloride	300 mg.
Pyridoxine	5 mg.	Polysorbate 80 U. S. P. (tween 80 †)	100 cc.

* This special vitamin mixture was furnished by The Lilly Research Laboratories through the courtesy of Dr. A. Lee Caldwell, Head, Nutrition and Vitamin Research Department, and Mr. Jean Q. Bellard.
† Registered trademark.

usually develops. That this is in part due to a hemolytic process is evident by the discoloration of the skin which is noticed after several weeks but before transfusions have been given and the deposition of hemosiderin noted in the internal organs when they are examined microscopically. In addition, the vascular necrosis in the bowel observed in malignant hypertension may also result in a loss of large amounts of blood. The resulting anemia may be of sufficient degree to cause death of the animal unless counteracted by blood transfusion. In our series of dogs it has usually been necessary to give transfusions to the animals an average of once every 10 days to maintain a normal hemoglobin content.

RESULTS

The Peritoneum as a Semipermeable Membrane.—The rapidity with which substances, such as urea, pass from the blood into the peritoneal cavity is demonstrated in figure 2, which shows the urea content of the peritoneal fluid at various times following the injection of 1 liter of a solution containing varying concentrations of glucose. As noted from this figure, equilibrium is complete in about two hours. Essentially the same time is necessary in the human subject when 2 to 3 liters is introduced into the peritoneal cavity, and similar results are obtained when one determines the rate of passage of electrolytes, creatinine, glucose or nonprotein nitrogen across the peritoneum.

That the serous lining of the peritoneum retains its semipermeable properties when subjected to the conditions used in the present study for long periods is

demonstrated in table 3 in which analytical data on blood and peritoneal fluid taken simultaneously are recorded. As is evident from the table, equilibrium across the peritoneum is attained as would be anticipated from an inert semipermeable membrane. The protein (0.1 per cent or less) which appears in the peritoneal fluid is also evidence for the high degree of permeability of the peritoneum. The fact that dogs survive for prolonged periods in good condition indicates that no appreciable accumulation of toxic catabolites occurs.

The discrepancies between the concentration of electrolytes in the blood and that in the peritoneal fluid shown in table 3 are explicable on the basis of the

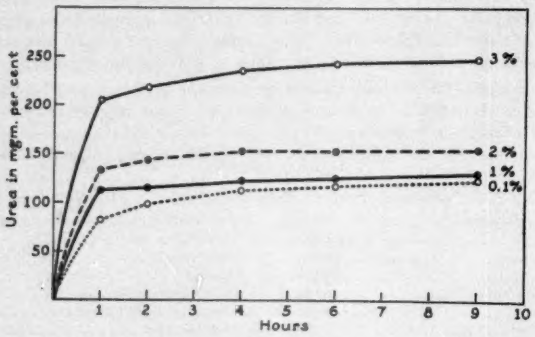

Fig. 2.—The rate of passage of urea into the peritoneal fluid of a dog after the injection of 1 liter of solution (table 1) containing the amount of glucose indicated at the right of the curves.

TABLE 3.—*Comparison of the Composition of the Blood and Peritoneal Fluid* *

Days After Nephrectomy	Urea, Mg./100 Cc.		Chloride, mEq./L.	
	Blood	Peritoneal Fluid	Blood	Peritoneal Fluid
5	106	116	97	98
10	152	163	101	103
20	202	238	100	101
30	220	250	100	99
40	228	230	97	98
50	171	162	100	101

* Samples were taken simultaneously three hours or more following the injection of the fluid of table 1 into the peritoneum.

Donnan equilibrium. In the case of urea, however, the paradox of a higher concentration appearing in the peritoneal fluid than in the blood is explained by the high protein content of the blood plasma compared with the minimal amount present in the peritoneal cavity and by the fact that urea in aqueous solution is associated to a greater degree than it is in the presence of blood.[21]

Factors Determining the Passage of Fluid Across the Peritoneum.—Although the peritoneum is freely permeable to glucose, the presence of a hypertonic solution in the peritoneal cavity will abstract fluid from the blood because of the more rapid rate of diffusion of water and electrolytes as compared with the

21. Grollman, A.: The Vapour Pressures of Aqueous Solutions with Special Reference to the Problem of the State of Water in Biological Fluids, J. Gen. Physiol. **14**:661, 1931.

slower rate of the larger glucose molecules. This fact is made use of to prevent overhydration after the introduction of protein-free fluids into the peritoneal cavity and to permit hydration if dehydration of the tissues is present.

Since glucose is depended on to determine the total fluid exchange across the peritoneum, a knowledge of the rate of its disappearance from the lavage fluid is important in determining the time during which this should be allowed to remain in the peritoneal cavity. As shown in table 4, the volume of fluid remaining in the peritoneal cavity after injecting 1 liter is determined by the original glucose content (which determines the direction of flow across the peri-

TABLE 4.—*Average Volume of Fluid Obtained with Variable Concentrations of Glucose and Variable Periods of Time Following the Injection of One Liter Intraperitoneally*

No. of Dogs	Type of Dog	Concentration of Glucose, %	After 8 Hr.	After 16 Hr.
2	Normal controls	3	970 (34) ± 39 *	640 (35) ± 45 *
5	Anuric	3	1,086 (116) ± 26	848 (122) ± 30
3	Anuric	1.5	914 (36) ± 29	801 (25) ± 75
1	Anuric	0.1	760 (48) ± 21	606 (3) ± 48

* Standard error. The number of observations on which the averages given in the table are based are given in parentheses.

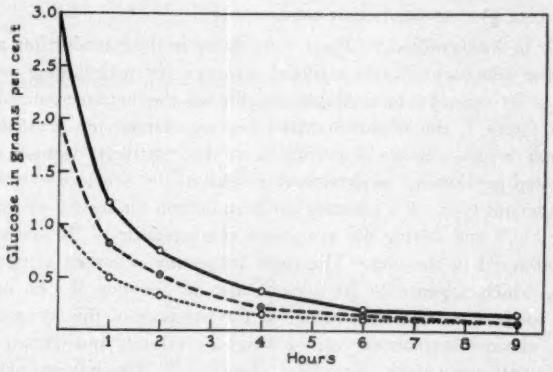

Fig. 3.—The rate of disappearance of glucose from 1 liter of fluid (composition as in table 1) when introduced into the peritoneal cavity of a 10 Kg. dog. The three curves are based on solutions originally containing 3.0, 2.0 and 1.0 per cent glucose, respectively.

toneal membrane) and the time the fluid remains in the peritoneal cavity. As shown in figure 3, the excess glucose disappears from the peritoneal cavity during the course of two to six hours, depending on its original concentration. At a concentration level of 2 or more per cent, there is a passage of fluid from the tissues into the peritoneal cavity. After several hours, when the glucose level has been reduced, the direction of flow is reversed and fluid now passes from the peritoneal cavity into the blood stream. Eight hours following the injection of 1 liter of solution containing 3 per cent glucose, one may remove 86 cc. more fluid from the peritoneal cavity than was originally injected. On the other hand, if the original solution contained only 1.5 per cent glucose, 86 cc. will be

absorbed; whereas if only 0.1 per cent of glucose was originally present about 250 cc. will be absorbed. As is to be anticipated, after 16 hours increasingly smaller volumes are recoverable, as shown in the last column of table 4. In the case of the normal animal (line 1, table 4) excretion by the kidney expedites the removal of fluid from the peritoneal cavity so that even after eight hours appreciable amounts of a solution originally containing 3 per cent glucose have been absorbed.

As is evident from table 4, it is possible to add or remove fluid from the body by alteration of the glucose content of the lavage fluid. When two lavages are done daily, the use of 1.5 per cent glucose solution will maintain a relatively normal water balance. Should dehydration appear, this is reduced to 0.1 per cent, whereas in the presence of overhydration a 3 per cent solution is used. In the case of the human patient, glucose concentrations as high as 5 and 7 per cent were used in two cases in which there was severe peripheral and pulmonary edema secondary to congestive heart failure. On the disappearance of this edema, the glucose content was reduced to 3 per cent, the concentration which was used in the other patients treated. At autopsy, the patients revealed no evidence of irritation of the peritoneum attributable to the use of the hypertonic glucose solution. When only moderate dehydration is desired, a 3 per cent glucose content is desirable because this results in the maintenance of a relatively constant fluid volume in the body with only slight dehydration. When it is desired to hydrate the patient, a 0.1 per cent glucose solution is used.

Results in Nephrectomized Dogs.—As stated in the introduction, an unequivocal test for the adequacy of any artificial measure for maintaining renal excretory function is its capacity to maintain the life of the nephrectomized animal. As shown in figure 1, the nephrectomized dog maintained for a month or more by intermittent lavage appears superficially to be relatively normal. However, as demonstrated previously,[3] nephrectomy results in the development of hypertension of the malignant type. On pathological examination the lesions of this disorder are demonstrable,[22] and during life symptoms characteristic of the disease in man are also encountered in the dog. The most frequently observed symptom in man is headache, which appears to be present also in the dog if one may accept the tendency to rub the head as evidence of the presence of this symptom. Dyspnea, dizziness, visual disturbances, loss of weight, weakness and nausea and vomiting, other common presenting symptoms observed in the human patient, are also encountered in the dog accompanying the elevated blood pressure induced by nephrectomy.

Despite the abnormalities just cited, which we believe to be due to the exclusion of other than the excretory function of the kidney,[23] survival of the nephrectomized dog for periods several times as long as that ever previously reported using peritoneal lavage,[24] the artificial kidney,[5] or other means has been attained as

22. Muirhead, E. E.; Grollman, A., and Vanatta, J.: Hypertensive Cardiovascular Disease ("Malignant Hypertension"): Changes in Canine Tissues Induced by Various Manipulations of the Kidney, with Special Reference to Vascular and Myocardial Lesions, Arch. Path. **50**:137 (Aug.) 1950.

23. Grollman, A.: Experimental Studies on Hypertension, in Symposium on Hypertension, Minneapolis, University of Minnesota, to be published.

24. Seligman and others.[8] Abbott and Shea.[6] Bliss and others.[7]

shown in table 5, in which pertinent data are given for seven nephrectomized dogs that we have studied. All dogs survived 30 days or more, as compared with 19 days, the maximum reported previously in the literature,[3] and two were killed on the thirty-ninth and seventieth days following removal of the kidneys. Contributing factors (last column) to the death of two dogs 31 and 34 days following nephrectomy was the development of spirochetal jaundice (due to infection by Leptospira icterohaemorrhagiae and Leptospira canicola) which is common in this area. Three of the animals manifested partial intestinal obstruction, which may be attributed in part to the effect of peritoneal irritation or infection by organisms of low grade pathogenicity.

TABLE 5.—*Survival Period of Seven Bilaterally Nephrectomized Dogs Subjected to Intermittent Peritoneal Lavage*

Dog No.	Body Wt., Kg.		Survival Period, Days	Accessory Autopsy Observations
	Original	Final		
10	7.4	5.6	34	.....
14	8.0	5.2	69 *	Partial intestinal obstruction
16	9.9	7.7	40	Partial intestinal obstruction
19	10.4	9.7	38 *	.....
23	7.8	6.7	34	Spirochetal jaundice
29	10.8	8.7	31	Spirochetal jaundice
42	8.2	5.8	30	Partial intestinal obstruction

* Killed.

TABLE 6.—*Concentration of Electrolytes in Blood Plasma of Bilaterally Nephrectomized Dogs Subjected to Intermittent Peritoneal Lavage* *

Dog No.	Days After Nephrectomy	Na	K	Ca	Mg	Cl	HCO_3
1	8	149	4.5	4.4	1.2	105	20.0
	10	149	5.0	4.8	1.6	108	19.4
14	10	146	3.3	4.2	1.3	100	18.8
	30	143	3.5	4.7	1.6	102	19.0
	50	148	4.0	4.8	1.3	103	21.0
	69	145	2.5	4.5	1.4	101	22.2
19	12	146	4.2	4.6	1.7	104	21.1
	34	148	4.4	5.0	1.6	105	20.0
42	16	142	3.3	4.0	1.0	103	21.6
	19	146	4.5	4.5	1.3	98	18.0

* All values are expressed in milliequivalents per liter.

The blood levels of electrolytes and of the nonprotein nitrogenous and other catabolic constituents of the blood plasma in dogs maintained by intermittent peritoneal lavage are shown in tables 6 and 7. The electrolyte pattern as shown in table 6 is relatively normal, but the levels of urea and other catabolites as shown in table 7 are considerably above normal when the simplified procedure as outlined is used. However, by repeated lavage at two hourly intervals during the day, it is possible also to maintain these at more normal levels when so desired.

Results on Patients.—In table 8 are summarized the pertinent data on five patients in whom the application of our procedure resulted in a definite reduction in the elevated urea and creatinine content of the blood and a correction of its

abnormal electrolyte pattern. In patient 1, admitted in a state of semicoma (hypertensive encephalopathy), a striking amelioration occurred after 16 hours of lavage, at which time diuresis set in and the procedure was, therefore, terminated. This patient has returned to work and is now being maintained on a drastic salt-restricted diet.

Patient 3 was also in a state of semicoma, with cyanosis and pulmonary and peripheral edema. The electrocardiogram revealed a grossly irregular nodal rhythm with auriculoventricular dissociation, frequent ventricular premature beats and left axis deviation. Within 24 hours after the beginning of the lavage, the patient regained consciousness, the edema and generalized anasarca had disappeared and the electrocardiogram now revealed normal sinus rhythm. The patient maintained his improved state for three days following cessation of the lavage, gradually became comatose again and died five days later.

Patient 4 was in a state of deep coma with generalized tremors and convulsive movements at the initiation of the lavage. Pulmonary edema necessitated repeated suction of the tracheal contents. After 24 hours, he had regained consciousness,

TABLE 7.—*Concentration of Nonprotein Nitrogenous and Other Catabolic Constituents of Blood Plasma of Bilaterally Nephrectomized Dogs Subjected to Intermittent Peritoneal Lavage* *

Dog No.	Days After Nephrectomy	Urea	Nonprotein Nitrogen	Creatinine	Inorganic Phosphate	Inorganic Sulfate	Phenol
1	10	122	68	7.2	7.0	1.5	2.0
3	10	185	95	4.7	9.0	5.0	2.4
6	15	135	71	7.1	7.1	3.4	3.4
14	50	154	82	5.3	6.9	2.6	2.5
28	34	190	70	5.8	6.0	3.0	2.5
29	18	198	116	9.7	7.3	2.9	2.8

* All values are expressed in milligrams per 100 cc.

the muscular movements had ceased and all evidence of pulmonary edema had disappeared.

Improvement in the clinical condition of the other two patients was not striking. They died five and 12 days after termination of the lavage, which cannot be considered as life saving in the presence of irreversible renal damage.

COMMENT

The efficacy of intermittent peritoneal lavage as a means of prolonging the survival of the bilaterally nephrectomized dog is demonstrated by the results of the present study. Not only is the procedure as described relatively simple but the condition of the animals is better and the period of survival is several times that attained by the application of the more complex artificial kidney. Although the application of the procedure to the human being has thus far been limited to only five patients, the results obtained on these subjects, as well as the results on the dog, suggest that the method as outlined may be of value in such patients as require the use of an artificial means for removing excess waste products or adjusting alterations in water, electrolyte and acid-base balance in the body. When properly managed *ab initio,* it is now recognized that conservative measures alone suffice in the management of most patients with acute anuria due to reversible renal damage.[2] However, in patients in whom early treatment has been ill advised, the

TABLE 8.—*Chemical Changes in the Blood of Five Anuric Patients Subjected to Intermittent Peritoneal Lavage*

Patient No.	Age and Sex	Diagnosis	Blood Pressure, Mm. Hg		Duration of Lavage, Hr.	Urea, Mg./100 Cc.		Creatinine, Mg./100 Cc.		Na, mEq./L.		K, mEq./L.		Cl, mEq./L.		CO_2 Combining Power, mEq./L.	
			Before	After		Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
1	.. ♀	Hypertensive cardiovascular disease	300/170	170/120	16	142	87	6.7	4.0	148	140	6.1	4.0	100	95	18	29
2	43 ♂	Chronic nephritis	95/60	100/70	36	312	204	13.8	6.6	152	146	7.2	4.6	105	100	12	25
3	53 ♂	Hypertensive cardiovascular disease	130/100	140/90	30	240	130	3.8	2.8	137	144	5.0	4.2	81	98	19	29
4	62 ♂	Chronic nephritis	230/130	170/110	48	306	98	12.0	4.8	128	148	7.8	4.1	85	100	15	27
5	48 ♂	Hypertensive cardiovascular disease	270/170	200/140	48	284	173	9.9	6.4	140	145	7.6	3.8	85	100	25	30

use of artificial measures may be indicated and the procedure of intermittent lavage as described offers many advantages over the artificial kidney. The use of the latter not only imposes the strain of an arteriovenous fistula but requires a complex apparatus, a staff skilled in its operation, cannulation of blood vessels, a supply of blood to fill the apparatus, etc.[25] The apparatus and materials needed in the procedure which we have outlined are available in every hospital, and only a simple paracentesis is involved. Possible applications of the procedure may be found in profound disturbances of water and electrolyte metabolism, in pulmonary edema and congestive failure not responding to the usual therapeutic measures, in acute hypertensive encephalopathy and as an investigative tool in other clinical states.

Exchange transfusion, which has been used and advocated by French workers,[26] suffers from the objection that it is expensive, requires large volumes of blood and may lead to serious reactions. In our experience with this procedure in dogs, the method has been less satisfactory than peritoneal lavage and has been accompanied with systemic reactions despite careful cross matching of the blood of donor and recipient. The chief objections raised against the use of peritoneal lavage in the past have been the risk of peritonitis, irritation of the peritoneum by the use of hypertonic solutions and the formation of fibrinous exudate which decreases the efficiency of the serous membrane as a dialyzing membrane. On the basis of our experiments, we feel that these objections have been exaggerated. In none of the patients whom we have treated has infection occurred as determined by culture of the peritoneal fluid or as observed at autopsy. In the case of dogs in which lavage has been continued for as long as 70 days, infection has been observed only once. In this case, peritonitis followed a failure to observe the usual precautions for maintaining asepsis. There has been no evidence of a decrease in the efficiency of the peritoneum as a semipermeable membrane even when the procedure has been performed for many weeks.

The intermittent procedure just described avoids the complex apparatus, multiple incisions and constant attention necessary when one utilizes a constant perfusion technic as advocated by previous investigators. It is, nevertheless, almost equally effective as a means of replacing renal excretory function since, as shown in figure 2, it requires several hours for equilibrium to be established between fluid in the peritoneum and the blood. A continuous lavage tends, moreover, to result in channeling of the perfusion fluid and hence may actually prove less efficient than an adequate emptying of the peritoneal cavity intermittently by the procedure which we have described.

SUMMARY

A method is described for intermittent peritoneal lavage which has been applied to the nephrectomized dogs and to a series of five patients. The use of the procedure has permitted the prolongation of the life of the dogs in good condition for periods of 30 to 69 days, which is several times that previously ever attained.

As applied to the human subject, the method has the advantage of simplicity and requires no special or complicated apparatus.

25. Merrill, J. P.; Thorn, G. W.; Walter, C. W.; Callahan, E. J., III, and Smith, L. H., Jr.: Use of the Artificial Kidney, J. Clin. Investigation **29**:412, 1950.

26. Dausset, J.: Lower Nephron Nephrosis: Report of Treatment of 44 Patients by Repeated Replacement Transfusions, Arch. Int. Med. **85**:416 (March) 1950.

DIFFUSE CALCIFICATION OF THE PANCREAS

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PANCREATIC calcification is a disease entity with a distinct clinical and pathological picture. It must be considered as a possibility in the differential diagnosis of abdominal pain. When the condition is looked for carefully by means of roentgenography, the diagnosis can be established in a greater number of cases than previously reported. Since there are few laboratory findings other than roentgenographic appearance and changes in the serum amylase level to help localize the disease to the pancreas, it is imperative that accurate history, physical examination and clinical judgment be used to help make a positive diagnosis.

Description of stones in the pancreas excited the interest of physicians as early as the seventeenth century. DeGraaf [1] spoke of the condition in 1667. Oser [2] stated that this report was followed by the publications of Bonetus in 1700, Galeati in 1757 and Morgagni in 1765. Thomas Cowley, also cited by Oser,[2] described in 1788 a case of diabetes in a 34 year old man who showed a pancreas impacted with calculi. In the files of autopsy material from Johns Hopkins Hospital,[3] there was a record of a case in 1891, with death occurring from pulmonary tuberculosis. Oser [2] listed the reports of 70 known cases of pancreatic calculi up to 1903. In 24 per cent of these cases glycosuria was present. Allen [4] has been credited with the description in 1903 of the first case of diffuse pancreatic lithiasis with complete clinical and pathological study. Since then, many similar cases have been described.

The incidence of pancreatic stones as encountered in the general pathological material is low, as cited by Pascucci.[5] Among 117,031 routine autopsies 52 cases

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1. Cited by Rockwern, S. S., and Snively, D.: Pancreatic Lithiasis Associated with Pancreatic Insufficiency and Diabetes Mellitus, Arch. Int. Med. **65**:873-881 (May) 1940.

2. Oser, L.: Diseases of the Pancreas, in Nothnagel, C. W. H.: Encyclopedia of Practical Medicine, Philadelphia, W. B. Saunders Company, 1903, p. 223.

3. King, A. B., and Waghelstein, J. M.: Calcification of the Pancreas, Arch. Int. Med. **69**:165-176 (Feb.) 1942.

4. Allen, L. W.: Chronic Interlobar Pancreatitis with Pancreatic Calculi, Ann. Surg. **37**:740-745 (May) 1903.

5. Pascucci, L. M.: Pancreatic Cyst and Lithiasis, Am. J. Roentgenol. **52**:80-87 (July) 1944.

were found, an incidence of 0.004 per cent. Lüdin [6] stated that on the basis of roentgenograms taken of the pancreas before dissection stones were demonstrated in 5.1 per cent of cases.

Mayo [7] spoke of two types of calcium deposits in the pancreas, true stones in the ducts and false stones or calcifications of the parenchyma. Beling [8] suggested that a distinction be made between disseminated calcification of the pancreas and the usual form of pancreatic lithiasis. He regarded the former as a distinct clinical entity. It has further been suggested [9] that another category be added, namely, mixed calcification of the pancreas, in which there are both parenchymal and intraductal calcifications. These suggestions, we feel, would only add confusion to a problem which, in itself, is complex and badly in need of simplification.

Stones in the pancreas may be either intraductal or parenchymal. The intraductal stones are usually solitary and may be the only evidence of calcification. When diffuse calcification is present, it is our opinion that the clinical, roentgenologic and pathological picture is the same as that of so-called disseminated calcification of the pancreas, mixed calcification or multiple stones. Therefore, calcific deposits in the pancreas should be classified either as solitary stones or as diffuse calcification. In our opinion, diffuse calcification of the pancreas is a clinicopathological entity encompassing multiple calculi spread widely within the pancreas, with fibrosis, inflammation and parenchymal damage. The pancreas may vary in size but is usually atrophic. The exploring surgeon, as a rule, feels a firm gland or sac of gravel and stones. The calculi are found to be within the ducts or in the immediate vicinity of dilated ducts or pseudocysts. The widened ducts often contain thickened pancreatic secretion. Microscopically, an intense fibrosis replaces the serous and islet tissue. Collections of polymorphonuclear cells, lymphocytes or histiocytes are observed in the interstices. Calculi are found either in larger or finer duct radicles or in spaces without perceptible epithelial lining.

During a period of two years we have collected a series of 21 cases of diffuse pancreatic calcification. Of these patients six died and were studied at autopsy. In another case a specimen of pancreas was available for study after surgical resection. In the 18 patients under our personal observation serum amylase determinations, dextrose tolerance tests when necessary, stool examinations and roentgen examinations were done. Several had the Schmidt nuclear test, which consists of oral administration of a small piece of thymus wrapped in gauze. The specimen recovered from the stool is studied histologically for evidence of nuclear autolysis due to pancreatic enzymatic action. In several patients fractional serum amylase levels were determined after the injection of a neostigmine (prostigmin®) salt.

PRESENTATION OF CASES

The patients can be divided into those who had the disease without any symptoms suggestive of pancreatic involvement and those with symptoms pointing to the

6. Lüdin, M.: Die Röntgendiagnostik bei Pankreasaffektionen, Arch. f. Verdauungskr. **63**:273-291 (Nov.) 1938.

7. Mayo, J. G.: Pancreatic Calculi, Proc. Staff Meet., Mayo Clin. **11**:456-457 (July 15) 1936.

8. Beling, C. A.: Calcification of the Pancreas, Am. J. Digest. Dis. **7**:231-234 (June) 1940.

9. Domzalski, C. A.: Calcareous Pancreatitis, Ann. Int. Med. **31**:650-660 (Oct.) 1949.

pancreas as the seat of trouble. In the first group there were three patients, two of whom had preexisting diabetes but no symptoms from their pancreatic disease. In these two patients the existence of the calcification was discovered by roentgenography in a survey of 100 diabetics. In the third patient the disorder was discovered at postmortem study. In the second group there were 18 patients who had one or a number of symptoms referable to the pancreas.

The addendum includes the history and clinical findings on the patients studied. In this series we find a total of 16 with diabetes, the presence of which was proved by either abnormal dextrose tolerance curves and glycosuria or high fasting blood sugar levels and glycosuria. Of the total, 18 patients were alcoholics, 15 of whom could be classified as heavy drinkers, the others as moderate drinkers. Three of the patients denied habitual use of alcohol. Tuberculosis, either active or in the past history, was recorded for four patients. Pain was the outstanding symptom in 17 patients. Abnormal stools were noted for only five persons, two of whom had as their only symptom abnormal and frequent bowel movements. Postmortem examinations were performed in cases 3, 6, 9, 15, 17 and 21. Partial resection of the pancreas was done in case 1. Another patient (case 2) had resection of the pancreas with removal of many stones. In a third patient (case 7) splanchnicectomy was performed. Three patients (cases 5, 7 and 19) were operated on for pancreatitis. No biopsy specimens were available from any of these. All the patients had the antemortem diagnosis established by roentgenography, with the exception of one (case 17) in whom calcification was first discovered at postmortem examination.

The following case reports were selected as being representative of the variable clinical pictures presented by the disease.

CASE 12.—*Diabetes mellitus; asymptomatic pancreatic calcification found in roentgenographic survey.*

A 38 year old white man was admitted to the hospital on Dec. 2, 1947. He had been a known diabetic for seven years, and his disease was controlled with a diet of 130 Gm. of carbohydrate, 110 Gm. of fat and 90 Gm. of protein and with administration of 25 units of protamine zinc insulin and 42 units of regular insulin daily. A carbuncle on his neck had been incised and drained a year previously. He drank alcohol occasionally. His father had been diabetic and died of cancer. The results of systemic review were noncontributory. The patient denied any gastrointestinal disturbance. Physical examination revealed a well developed and well nourished white man without any significant abnormalities. A scout film of the abdomen (fig. 1) showed calcific deposits in the region of the pancreas. A roentgenographic study of the gastrointestinal tract localized the deposits to the pancreas. Calcification of vessels of legs and feet was seen on roentgenograms. A barium sulfate enema study, gallbladder series and intravenous pyelograms revealed no evidence of calcific deposits.

The blood sugar levels varied from 130 to 250 mg. per 100 cc. Glycosuria was present when the diabetes was not under satisfactory control. Blood serum amylase values ranged from 40 to 50 mg. per 100 cc. The Schmidt nuclear test revealed evidence of digestion of the cells of the ingested thymus, indicating activity of pancreatic enzymes. Stool examination disclosed some meat and vegetable fibers, together with starch granules. The sedimentation rate was 6 mm. (Westergren) in one hour. Wassermann and Kahn reactions were negative. The hemoglobin concentration was 17.5 Gm. per 100 cc., and white blood cells numbered 7,800 per cubic millimeter.

In contrast to the above patient others had severe pain as a result of their disease.

The following case report demonstrates the chronicity of the disease and the type and severity of pain.

CASE 18.—*Diabetes mellitus, recurrent pain, alcoholism, calcification of pancreas for thirteen years.*

A. T., a 55 year old white male reporter, entered the hospital on numerous occasions from 1937 through 1949. He gave a history of active pulmonary tuberculosis in 1918 with discharge after five months on arrest of the disease. His next admission to a hospital was in 1928, when he had a ruptured appendix. He was an excessive drinker for 25 years and was in a sanatorium on several occasions for treatment of alcoholism. In 1934, during one of his hospitalizations for alcoholism, jaundice developed and he was found to have enlargement of the liver. In 1937, on the basis of polydipsia, polyuria and weight loss of 20 pounds (9 Kg.), a diagnosis of diabetes was established. It was at this time that he was seized with severe, generalized, cramplike abdominal pain which neither radiated nor was accompanied with nausea or vomiting. A study

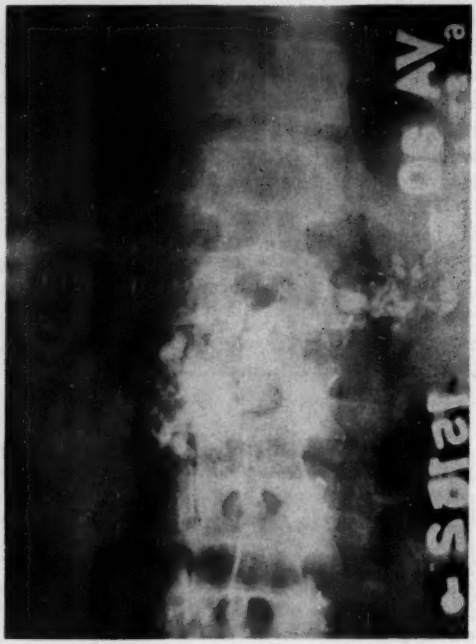

Fig. 1 (case 12).—Roentgenogram of the pancreas showing diffuse calcification.

of gastrointestinal roentgenograms revealed fine small areas of calcification in the left upper abdominal quadrant extending transversely across the level of the first lumbar vertebra. A chest roentgenogram showed no evidence of pulmonary tuberculosis. From that time he continued to have "gas pain" around the umbilicus which came on several minutes after meals and was relieved by use of sodium bicarbonate. In 1944 the pain had no definite relationship to meals and began to radiate to both sides and into the back. Another roentgenologic study of the gastrointestinal tract revealed an increase in the calcific deposits in the pancreas.

His next admission to the hospital was in May 1947. The pain had increased in severity during the preceding eight months and was not relieved by taking sodium bicarbonate. In addition to the abdominal pain, he also had sharp pains in both lower extremities.

The positive physical findings were as follows: The patient was well developed and undernourished. The eyegrounds disclosed early arteriosclerotic changes. There was absence of pulsations in the dorsalis pedis and posterior tibial arteries bilaterally.

A cholecystogram showed no evidence of biliary calculi. A gastrointestinal series disclosed no involvement of the esophagus, stomach, duodenum or bowel but revealed calcification of the pancreas. An intravenous pyelogram showed no stones in the kidney.

Results of Laboratory Examinations.—The sedimentation rate was 4 mm. in one hour (Westergren). The hemogram was normal. Tests revealed no evidence of impairment of liver function. Stool examination disclosed a few meat fibers and no excessive fat globules. The serum amylase range was from 40 to 50 mg. per 100 cc. The blood cholesterol was 214 mg. Blood sugar values varied from 77 to 200 mg. Ingested thymus showed destruction of only a few peripheral nuclei, pointing to a decrease of proteolytic enzyme activity.

Comment.—The patient underwent chordotomy for relief of pain in the legs, which were later amputated. He was a drug addict and had marked peripheral neuritis.

The pain in calcification of the pancreas may imitate that in many diseases. Likewise, other conditions may exist, and the incidental finding of calcific deposits in the roentgenogram may lead one to make an erroneous diagnosis. The following case illustrates the many other diseases that may coexist with calcification of the pancreas and the conditions it may simulate. The report also demonstrates the need for complete and careful study.

CASE 3.—*Diabetes, alcoholism, involvement of entire hepatopancreatic system, symptoms of calcification of pancreas.*

This patient was a 49 year old white man who entered the hospital for the first time in 1933. At that time he complained of colicky pain in the right upper abdominal quadrant, which radiated into the back, with vomiting, heartburn, anorexia and belching. No roentgenogram of his abdomen was taken at that time. In 1935 he entered with similar complaints, and a roentgenogram revealed evidence of pyloric obstruction with a suggestion of peptic ulcer. In 1938 he returned because of severe vomiting. Extrarenal azotemia developed, with a rise in the nonprotein nitrogen level to 143 mg. per 100 cc. The blood sugar value during an episode of acute abdominal pain was 300 mg. A dextrose tolerance test two weeks later revealed 163 mg. of blood sugar on fasting, 192 mg. at one hour, 163 mg. at two hours and no glycosuria in any of the urine specimens. He was discharged feeling well but returned in 1940 because of abdominal pain. The final diagnosis at this admission was diaphragmatic pleurisy and pneumonia. He was discharged, only to return after several months because of pains in the right upper abdominal quadrant and epigastrium. A roentgenogram of the abdomen at that time revealed free air under the diaphragm and calculi in the pancreas which were mistaken for calcified lymph nodes. At surgical intervention a rupture of the gallbladder and a subphrenic abscess were found. After discharge he progressed satisfactorily until 1944, when he returned with complaints of abdominal pain and jaundice. A gastrointestinal study revealed the presence of a duodenal ulcer and calcification within the pancreas. His last admission was in 1947, when he entered because of fever and severe epigastric pain. Examination revealed a well developed, thin, emaciated, icteric man, with a mass in the epigastrium thought to be the liver. The results of liver function tests were normal. Serum amylase, which first measured 190 mg., rose to 270 mg. and dropped first to 103 mg., then to 66 mg., per 100 cc. The blood sugar was 120 mg. Serum protein was normal. Stool determinations showed no fat abnormality. Reactions to serologic tests were negative. At the surgical operation the pancreas was observed to be indurated and about three times its normal size with no evidence of abscess. The patient continued to have a spiking temperature elevation to 103 to 105 F. with pain. His course was progressively downhill. One month after surgical resection, an abdominal paracentesis was done and 1 liter of dark green fluid was withdrawn. Moderate distention of the abdomen continued, and later multiple fistulas opened at the site of previous surgical incisions. These drained fecal-smelling fluid and remained open until the patient's death on Jan. 24, 1948, six weeks after admission. The autopsy findings are reported in the presentation of the pathological material.

PATHOLOGICAL MATERIAL

The following seven case reports augment the pathological descriptions of Allen and others.

CASE 9.—*Calcification of pancreas, diabetes, pulmonary tuberculosis.*

At autopsy the pancreas weighed 240 Gm. and was firm. On cut section almost the entire parenchyma was replaced by fibrous grayish white tissue in which only minute elevated areas of residual pancreatic tissue remained. The main and smaller ducts were dilated and filled with pancreatic secretion. Within or near the ducts were multiple, firm, irregular, grayish white concretions ranging from 1 to 4 mm.

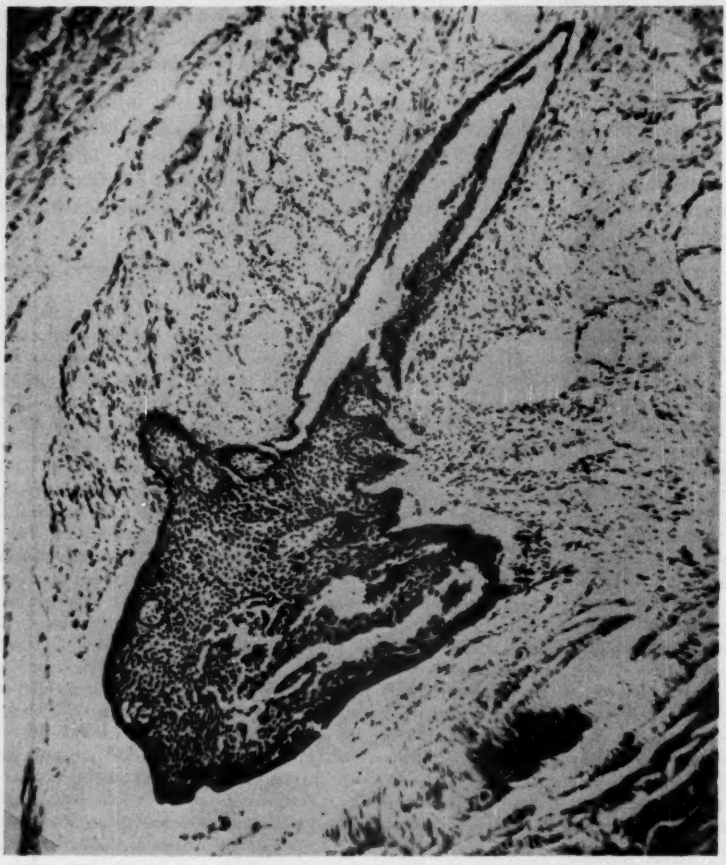

Fig. 2 (case 17).—Squamous cell metaplasia of pancreatic ducts.

Microscopic Observations.—A diffuse fibrosis with lymphocyte collections replaced the parenchyma. There was pronounced reduction of the serous glands and the islets. The dilated ducts in which stones lay contained denuded epithelium and polymorphonuclear cells. Some of the smaller spaces showed minute calculi with fibrin accumulations. That some of these spaces were ducts was indicated by the presence of desquamated epithelial cells. The blood vessels showed thickening of the walls. The nerves were surrounded by edema, fibrous tissue and lymphocytes. The stones were calcium carbonate in composition.

Within the lower lobe of the right lung a tuberculous abscess was noted. The gallbladder showed cholecystitis and cholelithiasis. The liver was normal.

CASE 15.—*Calcification of pancreas, diabetes, pulmonary tuberculosis.*

At autopsy the pancreas was considerably enlarged, firm and nodular. Multiple calculi up to 1 cm. were seen within dilated ducts. The pancreatic structure was obliterated with small, elevated nodular remnants.

Fig. 3 (case 17).—Photomicrograph of pancreas showing stone formation within a space that actually is a duct. Desquamated epithelial cells are within the lumen. Laminations of fibrin and calcium formed the stones.

Microscopic Observations.—There was diffuse fibrosis replacing the parenchyma, with occasional foci of islet and pancreatic tissue remaining. The interstices showed collections of lymphocytes. Some of the spaces in which the calculi lay were obviously ducts. Others were lined with necrotic debris and contained polymorphonuclear cells. The ducts were irregularly

grouped and contained a large number of mucous glands. The stones were composed of calcium carbonate.

The liver showed parenchymatous degeneration. Two stones were found in the gallbladder. The patient died of pulmonary tuberculosis.

CASE 17.—*Asymptomatic calcification of pancreas without diabetes.*

At autopsy the pancreas weighed 250 Gm. and was firm. On section the tissue was ivory white. Stones 3 to 4 mm. in size were found in dilated ducts and cystic spaces.

Microscopic Observations.—Although there was an increase of fibrous tissue, the serous glands and islets of Langerhans were only slightly depleted. On the other hand, the ducts were hyperplastic, formed pseudoadenomas and showed squamous cell metaplasia (fig. 2). The stones lay within dilated ducts and in spaces which apparently were interstitial. However, on careful search either duct lining or desquamated epithelial cells were seen, and this, we feel, indicates that these spaces formerly were ducts. The epithelial cells were mixed with fibrin and spicules of calcium (fig. 3).

The liver grossly and microscopically showed portal cirrhosis. The gallbladder was thickened, but no stones were present. The lung showed universal pneumonia with abscess formation.

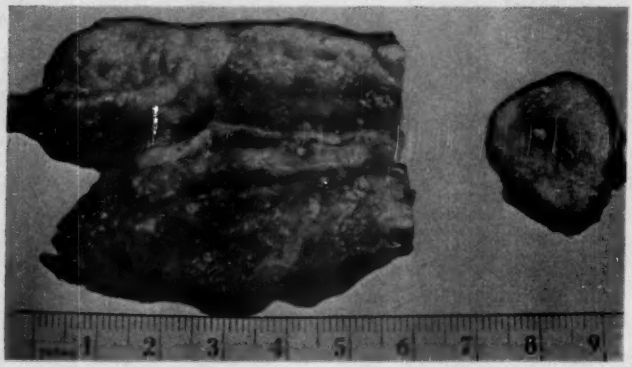

Fig. 4 (case 1).—Gross pancreas showing stones within the ducts and apparently within the tissues. Small nodules represent residual pancreatic tissue. Diffuse fibrosis is also present.

CASE 3.—*Calcification of pancreas, diabetes, involvement of entire hepatopancreatic system.*

At autopsy the pancreas was enlarged, firm and nodular. The ducts were dilated and filled with pancreatic secretion. The stones measured up to 8 mm. The common bile duct and the pancreatic duct were joined in a single outlet which was obstructed by a stone and fibrous tissue.

Microscopic Observations.—There was diffuse fibrosis with collections of lymphocytes, histiocytes and polymorphonuclear cells. The ducts were hyperplastic and dilated with calcium concretions. The parenchyma showed moderate atrophy. The stones were calcium carbonate on chemical examination.

Death was due to bile peritonitis resulting from perforation of the common bile duct. The liver showed ascending biliary infection with multiple abscesses and biliary cirrhosis.

CASE 6.—*Calcification of pancreas without diabetes, pancreatitis, abdominal abscesses.*

At autopsy the pancreas was slightly decreased in size, firm and pinkish gray. The lobular structure was intact. At the outlet of the pancreatic duct there was a calculus measuring 1 cm. The smaller ducts were dilated and filled with secretion and calculi. Stones were also observed within the pancreatic tissue.

Microscopic Observations.—Little distortion of the lobular architecture and only slight increase of interstitial tissue, accompanied with lymphocytes and monocytes, were noted. The arterioles were thickened and hyalinized. Stones were discovered in some of the ducts. The

cystic spaces contained necrotic epithelial cells and amorphous debris in some sections. Areas of enzymatic necrosis were present at the periphery.

In addition, there were fat necrosis of the omental fat and multiple abdominal abscesses with diffuse peritonitis. The liver showed portal cirrhosis. The stones were seen to be calcium carbonate on chemical examination.

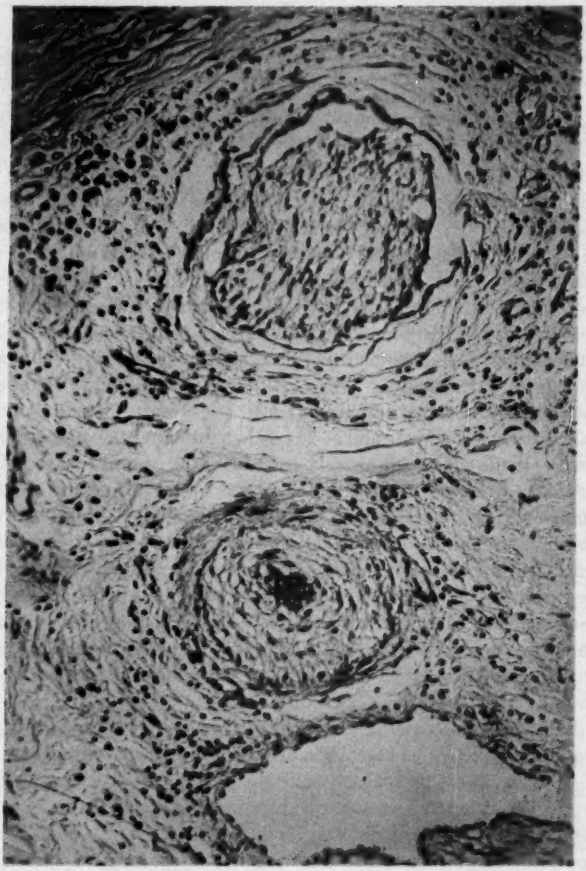

Fig. 5 (case 1).—Perineural fibrosis and lymphocytic infiltration of pancreas.

CASE 1.—*Diffuse calcification of pancreas, pancreatic abscess, surgical resection of pancreas.*

Gross Observations.—The pancreas had been enlarged, firm and nodular. Forty-two grams was removed surgically. Yellow nodules of pancreatic tissue protruded above the fibrous tissue. Dilated ducts contained calcium deposits (fig. 4).

Microscopic Aspects.—The dilated spaces were in part lined by ductile epithelium. Within the fibrous stroma were lymphocytic aggregates. The ducts were hyperplastic, although there

was moderate atrophy of pancreatic parenchyma. In addition to debris and desquamated epithelial cells, the ducts contained polymorphonuclear cells. Marked perineural fibrosis and lymphocytic infiltration were noted (fig. 5). The stones were calcium carbonate on chemical examination.

CASE 21.—*Diffuse calcification of pancreas, diabetes mellitus, myocardial infarction.*

At autopsy, grossly, the pancreas was atrophic, weighing 40 Gm. The entire organ was firm, with complete replacement of parenchymal tissue by fibrosis and small calculi. The large ducts were filled with similar stones.

Microscopic Observations.—Only small groups of distorted cells of pancreatic tissue were recognizable. A diffuse fibrosis accompanied with collections of lymphocytes remained. The nerves showed considerable perivascular fibrosis, often with foci of lymphocytes. Calculi were observed in the ducts and in the interstitial spaces.

The liver was unaltered. In the heart there were numerous infarctions due to coronary occlusion.

COMMENT

Although some authors believe that calcification of the pancreas is a result of chronic pancreatitis, it is difficult to relate pancreatitis to calcification in most of our cases. It may be impossible to elicit a history of the acute stage, as not all cases of pancreatitis have a fulminating course. Often the symptoms and signs last a few hours and subside, only to be diagnosed as indicative of some other intra-abdominal disease. In our series we had only two patients (cases 7 and 19) in whom the diagnosis of acute pancreatitis was made on surgical exploration prior to the finding of calcification. We were, however, unable to determine when calcification actually occurred in these patients. Comfort [10] reported the onset of calcification as early as one year and as late as 19 years after the onset of pancreatitis. There is basis for the contention that the calculi are the result of prior inflammation. Comfort [10] demonstrated that following chronic relapsing pancreatitis a pathological picture similar to the one we have described resulted in several of their cases. Stagnation of secretion and fibrosis within ducts resulting from inflammatory fibrosis may form the nuclei of stones. The pathological findings reveal two essentials to be intimately related: (1) multiple calculi and (2) inflammatory changes. One cannot conclude with certainty which is the initiating factor. Conceivably, stones within the duct may cause obstruction with inflammation subsequent to the stagnation. Yet experimental and pathological occlusion of the main duct does not necessarily result in diffuse calcification.

Four of our patients (cases 2, 13, 15 and 18) had tuberculosis, the disease being inactive in two and active in two. Baumel [11] in 1882 described a 50 year old man who died of tuberculosis and whose pancreas at autopsy was encrusted with fine concretions. Nevertheless, we do not feel that tuberculosis is a factor in the development of pancreatic calcification.

It is possible that alcoholism is a provocative factor in precipitating attacks of pancreatitis. Alcoholism was quite prevalent in previous reports and occurred in 18, or 85.7 per cent, of our patients.

The underlying pathophysiological process of calcification may be as described by Edmondson and his associates,[12] who felt that precipitation is due primarily to

10. Comfort, M. W.: Chronic Relapsing Pancreatitis: Its Clinical Course, Sequelae, Diagnosis and Medical Treatment in Cases in Which Disease of the Biliary or Gastro-Intestinal Tract Did Not Coexist, Proc. Staff Meet., Mayo Clin. **22**:548-552 (Nov. 26) 1947.

11. Baumel, cited by Oser,[2] p. 65.

12. Edmondson, H. A.; Bullock, W. J., and Mehl, J. W.: Chronic Pancreatitis and Lithiasis: Pathology and Pathogenesis of Pancreatic Lithiasis, Am. J. Path. **26**:37-56 (Jan.) 1950.

supersaturation of pancreatic juice with calcium carbonate. Pancreatitis with the presence of inflammatory debris, cystlike dilatation of ducts and stasis may presumably initiate the precipitation of calcium carbonate during an acute attack. We agree with them that the previous concept of Edmondson and Fields,[13] that calcification may follow fat necrosis, is not tenable, because this theory does not explain the formation of intraductal stones, nor are stones found in the omental fat, a frequent site of fat necrosis.

Diabetes was present in 16, or 76.2 per cent, of the patients studied. Among 100 diabetics surveyed with a scout film of the abdomen, two cases of calcification of the pancreas were uncovered, together with one case of solitary stone. No doubt, the calcification of the pancreas causes a marked degree of interstitial pancreatic damage with progressive destruction of the islets of Langerhans. The functional capacity of the islet tissue is thus tremendously reduced, and this, we feel, eventually causes the diabetes. These cases of calcification, therefore, represent examples of an absolute insulin deficiency. It has been stated that approximately 90 per cent of the insular tissue of the pancreas must be destroyed or removed before diabetes appears. However, it is also entirely possible that with destruction of less tissue than this diabetes may result. This may happen if insular reserve is reduced and other factors are superimposed, such as prolonged hyperglycemia, obesity or infection. In this manner an additional strain is placed on the islet tissue. This stress, then, may lead to increased demands on and fatigue of the remaining islets and thereby cause diabetes mellitus.

The course of diabetes in our patients was similar to that in any other diabetic, with aggravations of the disease by infection, intercurrent illness or dietary indiscretion. The insulin requirement of the patients varied from 20 to 74 units.

Clinically, the picture presented by the patients appears to be dependent on the site and extent of pancreatic involvement. Epigastric pain with radiation into the back is the commonest symptom. The commonest distribution of pain is girdle-like, not dissimilar to that seen in tabetic crises. Some patients have more pain in the right upper abdominal quadrant, others in the midepigastrium and still others in the left upper quadrant. These variables are dependent on whether the head, body or tail of the pancreas is involved.

The pain is often of two types, constant and recurrent. Simulation of the pain of gastric crisis suggests nerve pain, which may be the basis for the constant pain. Baggenstoss[14] has suggested that perineural inflammation is the cause of pain. All our patients showed perineural involvement of some degree. Pain may be recurrent and may come from the acute episodes of relapsing pancreatitis.

The occurrence of gallbladder disease is more than coincidental. Although Comfort[10] considered it of no significance, Haggard and Kirtley[15] found gallstones

13. Edmondson, H. A., and Fields, I. A.: Relation of Calcium and Lipids to Acute Pancreatic Necrosis: Report of Fifteen Cases, in One of Which Fat Embolism Occurred, Arch. Int. Med. **69**:177-190 (Feb.) 1942.

14. Baggenstoss, A. H.: Chronic Relapsing Pancreatitis: Review of Pathologic Anatomy in Cases in Which Disease of the Biliary or Gastro-Intestinal Tract Did Not Coexist, Proc. Staff Meet., Mayo Clin. **22**:542-547 (Nov. 26) 1947.

15. Haggard, W. D., and Kirtley, J. A., Jr.: Pancreatic Calculi: Review of 65 Operative and 139 Non-Operative Cases, Ann. Surg. **109**:809-826 (May) 1939.

in 13.8 per cent of cases of pancreatic calculi. Four of five gallbladders examined in our series showed some form of involvement. The association of gallbladder disease and acute pancreatitis is commonly recognized. In spite of an apparent relationship, such as occurred in our case 3 with stones in the common duct associated with coexisting pancreatic and biliary disease, the significance of gallbladder disease in diffuse calcification of the pancreas remains indefinite.

Cysts and abscess formation are occasionally noted in this disease and are most likely the result of fibrosis, obstruction and secondary infection. Pancreatic abscess formation was present in two of our patients (cases 1 and 6).

Steatorrhea and creatorrhea have been reported; thus, the stools may be gray, frothy, bulky and rather foul. This finding was not common in our series, as only five patients (cases 2, 10, 13, 19 and 20) had bowel disturbances. Only three had the characteristic type of stool. Jaundice may be present if obstruction or inflammation of the biliary tract takes place. This, we feel, occurred in only one patient (case 3).

The occurrence of portal cirrhosis is frequent enough to warrant further comment. It is recognized that a definite but obscure relationship exists between the liver and the pancreas. Here again the question is raised whether there is a common causal factor, or whether one diseased organ influences the other. It is apparent that the incidence of alcoholism is high in these patients. Thus, the same morbid influences producing cirrhosis in alcoholics might cause changes in the pancreas. On the other hand, it may be possible that with pancreatic disease, in which there is poor intestinal absorption, the liver is deprived of some necessary dietary component, such as lipocaic.

The pulmonary involvement is also striking; two of the patients died from tuberculosis and one with a necrotizing pneumonia. The development of tuberculosis in patients with calcification of the pancreas has been recognized by most observers. Is there some other responsible factor, such as exists in fibrocystic disease of the pancreas? In a review of the lungs of our autopsied material, no unusual features presented themselves.

The symptoms of calcification of the pancreas simulated those of gallbladder colic, peptic ulcer, perforated viscus, appendicitis, severe gastritis and malingering. The pain was of such intensity and duration as to have caused two of our patients to become addicted to morphine because of their constant request for something to relieve the pain. As one reads through the case histories, nearly all the common causes of an acute abdominal condition are present at one time or another in association with calcification of the pancreas. It is because of this that we feel it is so important to be able to differentiate and arrive at a diagnosis of the true condition. A scout film of the abdomen may reveal pancreatic calcification. This, however, does not mean that the calcification is the cause of the abdominal complaints. Changes in the serum amylase level, on the other hand, may be the only evidence of pancreatic involvement. We wish to stress that only after exclusion of all the above mentioned conditions can one be certain that pancreatic calcification is the cause of the abdominal pain. In this way many patients will not be subjected to prolonged and erroneous treatment. With the recent advances in pancreatic surgery, partial or total pancreatectomy or splanchnicectomy may be helpful. Surgical procedures on the pancreas were done in two of our patients, one of whom

had temporary relief; the other has had relief during the last two years. A third patient underwent splanchnicectomy and has had relief of pain for approximately 18 months.

SUMMARY

Twenty-one cases of diffuse calcification of the pancreas are presented. The pathological studies on six autopsy cases and one surgical case are reported.

Common symptoms are recurrent epigastric pain with radiation to the back, weight loss and, in 76.2 per cent of cases, the presence of diabetes.

No distinction should be made among diffuse calcification, disseminated calcification, mixed calcification and multiple calculi since the pathological aspects and clinical course are similar.

The diagnosis is established by means of roentgenography.

Fluctuation in the levels of serum amylase indicates pancreatic disease.

The pathological findings are characterized by acute and chronic inflammatory changes, diffuse replacement fibrosis, pseudocysts, dilatation of ducts and intraductal calculi.

In patients with intractable pain splanchnicectomy or pancreatic resection should be considered.

ADDENDUM

CASE 1.—A white man, 32 years of age, drank alcohol only in moderate amounts. He was diabetic and showed symptoms of pancreatic calcification. The patient is alive at present.

History.—His first admission was on March 1, 1948, because of gastric pain radiating to the left shoulder, with vomiting of seven months' duration. An operation was performed for the abdominal symptoms. Results on examination of the surgical specimen are presented in the section on pathological material. The patient reentered the hospital on March 23, 1949 with pain in the left upper abdominal quadrant and drainage from the operative scar. A small cyst was aspirated. There was no bowel disturbance.

Results of Examination.—Examination on March 1, 1948 showed absence of breath sounds over the lower two thirds of the left side of the chest. There was a tender, firm mass in the splenic region. Results of examination on March 23, 1949 were essentially normal.

Results of Laboratory Studies.—The blood showed 251 mg. of glucose per 100 cc. and 14,000 white blood cells per cubic millimeter. The urine had a positive reaction for sugar. The sinus drainage gave a positive reaction for amylase. The test with ingestion of thymus showed complete autolysis. The preoperative dextrose tolerance test disclosed 107, 150, 182, 123 and 100 mg. per 100 cc. The urine was normal. The postoperative dextrose tolerance test showed 306, 408, 594, 594 and 480 mg. per 100 cc. The urine revealed 2+, 3+ and 4+ reactions for sugar. There was 238 mg. of serum amylase per 100 cc. The serologic reactions were negative.

Roentgenologic Appearance.—Roentgenograms on the first admission showed diffuse calcification of the pancreas. On the second admission the film revealed a fistula from the abscess to the pancreas. Roentgenograms of the chest were normal.

Comment.—Forty-two grams of the pancreas was removed surgically, with relief of pain. The insulin requirement, which was 10 units after surgical intervention, was increased to 10 units of protamine zinc insulin and 20 units of regular insulin on the second admission.

CASE 2.—A white man, 51 years of age, drank alcohol only on occasion. He was diabetic and displayed symptoms of pancreatic disease for which surgical treatment was given. He had had tuberculosis in 1921. The patient is presently alive.

History.—A history of epigastric pain, nausea and flatulence of more than 25 years' duration was obtained. Irregular epigastric distress relieved by eating had been present for 16 years. On April 10, 1941 the patient entered the hospital with colicky epigastric pain and vomiting which were treated for 30 hours with suction. The pain subsided with

distention of the small bowel. Diabetes developed in 1945, and the patient noted frothy, foamy stools and loss of weight.

Results of Physical Examination.—The patient was a thin, chronically ill man. The abdomen was soft but slightly tender in the epigastric region. The liver was nontender and palpable 1 fingerbreadth below the costal margin.

Results of Laboratory Studies.—The fasting blood sugar level was 177 to 220 mg. and the serum amylase 67 mg. per 100 cc. The stool had the appearance of peanut butter on occasion. The reactions to serologic tests were negative.

Roentgenologic Appearance.—The patient had had a gastrointestinal series made in 1941. No evidence of calcification was found. Diffuse calcification of the pancreas was discovered in 1948. In 1937 a roentgenogram revealed arrested inactive tuberculosis.

Comment.—The patient's diabetes was controlled with administration of 6 units of protamine zinc insulin and 14 units of regular insulin daily. Resection of the pancreas in 1943 for pancreatic lithiasis with removal of many stones gave relief for eight months. The patient is a drug addict.

CASE 3.—This case is described in detail in the text.

CASE 4.—A white man, 59 years of age, had diabetes and was an alcoholic. He had symptoms of diffuse pancreatic calcification. He is still alive.

History.—This patient was in the hospital repeatedly from 1938 through 1949. The diagnosis of chronic cholecystitis was made, but no evidence of inflammation was noted on surgical intervention. The patient had repeated episodes of midepigastric pain with vomiting lasting up to 10 days. In 1948 a meat ball was impacted in a hiatus hernia. His last admission in 1949 was because of upper abdominal pain radiating to the left costal margin. There was no bowel disturbance.

Results of Examination.—The patient had an inguinal hernia, arteriosclerotic heart disease and prostatic hypertrophy.

Results of Laboratory Studies.—Serum amylase measured 312 mg. per 100 cc. The dextrose tolerance test showed a blood sugar level of 110 mg. on fasting, 169 mg. at one-half hour, 219 mg. at one hour and 244 mg. at two hours. The urine specimens were normal except for a trace of sugar in the one taken at two hours.

Results of Roentgenologic Studies.—A gastrointestinal series showed a diaphragmatic hernia measuring 6 cm. Films also revealed a duodenal diverticulum and calcified pancreas. Roentgenograms of the chest were normal.

Comment.—This patient had many admissions to the hospital for abdominal pain, nausea and vomiting for which no cause was ever demonstrated. Nevertheless, it is felt that these symptoms were on the basis of calcification of the pancreas. At present the patient has a hiatus hernia which causes him pain other than that from the pancreas.

CASE 5.—A Negro man, 50 years of age, displayed symptoms of diffuse calcification of the pancreas and diabetes. He was an alcoholic and is alive at present.

History.—Distention of the abdomen developed in January 1949. The patient reentered the hospital in October 1949 with chills, fever and pain in the upper part of the abdomen. His past history revealed intermittent gas pains and pain across the epigastrium, radiating from the right to the left, present for 10 to 12 years. There was no bowel distention. The patient entered the hospital again on Feb. 22, 1950 with similar complaints.

Results of Examination.—The abdomen was distended with fluid. There was a ventral abdominal hernia.

Laboratory Studies.—Fluid removed on abdominal paracentesis in January 1949 had the appearance of chyle. The Wassermann and Kahn tests gave positive reactions. A dextrose tolerance test made at this time showed 103 mg. of sugar on fasting, 172 mg. at one-half hour, 167 mg. at one hour, 134 mg. at two hours, and 92 mg. at three hours. The serum amylase was 168 mg. per 100 cc. The stool showed no abnormalities.

On Feb. 22, 1950 a repeat dextrose tolerance test showed 126 mg. of sugar on fasting, 164 mg. at one-half hour, 214 mg. at one hour, 211 mg. at two hours and 174 mg. at three

hours. The urine specimens were normal except for 3+ and 4+ reactions for sugar in the last two specimens examined. The serum amylase, at first 98 mg., dropped to 26 mg. per 100 cc.

Roentgenologic Appearance.—Roentgenograms of the chest, kidneys, ureters and bladder were normal. The appearance on administration of a barium sulfate enema was normal. A roentgenogram revealed pancreatic calcification.

Comment.—The appearance on esophagoscopy was normal. Exploration of the abdomen revealed pancreatitis and a milky hemorrhagic fluid. The pancreas was enlarged. No biopsy specimen was taken.

CASE 6.—This alcoholic white man, 57 years of age, had symptoms of diffuse calcification of the pancreas, but he did not have diabetes. Autopsy observations are presented in the section on pathological material.

History.—The patient complained of severe generalized abdominal pain for three weeks. Later pain developed in the right lower abdominal quadrant. The diagnosis of pancreatic calcification was made in 1941. The patient drank 1 pint (473 cc.) of whisky daily. There had been no abnormal stools, and the loss of weight was moderate.

Results of Physical Examination.—An elevation in temperature to 101 F. was recorded. Telangiectasis and tenderness in the right lower abdominal quadrant were noted.

Results of Laboratory Studies.—The serum amylase was 290 mg. per 100 cc. The urine showed no reaction for sugar. Nonprotein nitrogen measured 32 mg. per 100 cc. Total protein was 5.7 Gm., with 2.7 Gm. of albumin and 2.3 Gm. of globulin. There was 1+ cephalin flocculation.

Roentgenologic Appearance.—Calcification of the pancreas was seen on roentgenograms in 1941.

Comment.—A retroperitoneal mass to the right of the pancreas had been drained. Pain in the right upper abdominal quadrant and the back was continuous. Abdominal distention occurred, and the patient died.

CASE 7.—This diabetic white man, 44 years of age, was an alcoholic. He displayed symptoms of calcification of the pancreas. He is alive at the present writing.

History.—The patient had had a perforated ulcer in 1944, epigastric pain in 1945 and acute pancreatitis in 1946, with surgical intervention. He complained of epigastric pain radiating into the back and the right upper abdominal quadrant of four months' duration. There had been a loss of weight of 20 pounds in 1949. No stool changes were apparent.

Results of Physical Examination.—Physical examination revealed no abnormality except for a palpable edge of the liver.

Results of Laboratory Studies.—The urine was normal, and the stool showed no free fat. Serum amylase measured 68.4 mg. per 100 cc. A dextrose tolerance test revealed a blood sugar level of 78 mg. on fasting, 174 mg. at one hour, 200 mg. at two hours, 183 mg. at three hours and 56 mg. at four hours. The thymus test showed complete digestion. A repeat dextrose tolerance test gave essentially the same results. The test for serum amylase after administration of a neostigmine salt showed 67.6 mg. on fasting, 66.9 mg. at one-half hour, 74.2 mg. at one hour and 76.8 mg. at 1½ hours. All serologic reactions were negative.

Roentgenologic Appearance.—Roentgenograms showed calcification of the pancreas. A gastrointestinal series and films of the gallbladder and the chest revealed nothing abnormal.

Comment.—Splanchnicectomy was performed, with removal of dorsal nerve roots followed by relief of pain. The diabetes was controlled by diet.

CASE 8.—A diabetic white man, 44 years of age, was an alcoholic and had symptoms of calcification of the pancreas. He is alive at present.

History.—This patient had five admissions for treatment of alcoholism from 1937 to 1943. From 1948 through 1949 he complained of polyneuritis, anorexia, weight loss, daily epigastric pain and nervousness.

Results of Physical Examination.—Examination revealed atrophic muscles in the legs. Reflexes were absent. The liver was palpable 3 fingerbreadths below the costal margin.

Results of Laboratory Studies.—A dextrose tolerance test showed 66.9 mg. of sugar on fasting, 222.2 mg. at one-half hour, 253.2 mg. at one hour, 184.4 mg. at two hours and 117.6 mg. at three hours. Glycosuria (4+) was present. The test for serum amylase after administration of a neostigmine salt revealed 66.5 mg. on fasting, 63.8 mg. at one hour and 73.1 mg. at 1½ hours. The thymus test showed no digestion. Reactions to serologic tests were negative.

Roentgenologic Appearance.—Calcification of the pancreas was seen on roentgenograms. The roentgenograms of the gastrointestinal tract, gallbladder and chest had a normal appearance.

Comment.—The diabetes was controlled by diet.

CASE 9.—A diabetic Negro man, 52 years of age, displayed symptoms of calcification of the pancreas. He was an alcoholic. Autopsy observations are reported in the section on pathological material.

History.—This patient had diabetes for 10 years and was hospitalized seven times for regulation. Each episode was preceded by periumbilical pain radiating into the back, nausea, vomiting and fever. He had asthmatic bronchitis for many years. An appendical abscess developed in 1948. No surgical treatment was given. He was admitted to the hospital in 1949 after a drinking spree. The blood sugar level was 28 mg. per 100 cc. Intravenous administration of dextrose solution failed to revive him, and he died.

Results of Physical Examination.—The patient was in a coma during his last admission, and no positive findings were noted. Examination at a previous admission disclosed epigastric tenderness and moderate abdominal distention.

Results of Laboratory Studies.—The stools revealed no abnormality. The results of liver function tests were normal. The thymus test was unsuccessful. Serum amylase measured 42 mg. Serum albumin was 4.16 Gm. and serum globulin 4.11 Gm. per 100 cc. The serologic tests on blood and spinal fluid gave negative reactions.

Roentgenologic Appearance.—Pancreatic calcification was noted in 1948. The roentgenograms of the chest, gastrointestinal tract, colon, kidneys, ureters and bladder were normal.

Comment.—The patient's diabetes was controlled initially with daily administration of 44 units of protamine zinc insulin. Later he needed 50 units of regular insulin and 24 units of protamine zinc insulin daily. He had diabetic acidosis once in 1948.

CASE 10.—An alcoholic white man, 63 years of age, revealed symptoms of calcification of the pancreas. He is alive at the present writing.

History.—The patient had diarrhea with mucus but no blood. There were three to six stools daily for two years. A loss in weight of 25 pounds (11.3 Kg.) occurred. The patient drank 1 to 1½ pints (473 to 710 cc.) of whisky daily for 20 years.

Results of Physical Examination.—The liver was 2 fingerbreadths below the costal margin. There were a few telangiectases.

Results of Laboratory Studies.—The results on liver function tests revealed no abnormality. The urine, blood count and sedimentation rate were normal. The dextrose tolerance test showed 77 mg. of sugar on fasting, 122 mg. at one-half hour, 106 mg. at one hour, 106 mg. at two hours and 99 mg. at three hours. Serum amylase measured 30 mg. per 100 cc. Fractional studies with administration of a neostigmine salt revealed serum amylase levels under 40 mg. per 100 cc.

Roentgenologic Appearance.—Studies of the upper and lower parts of the gastrointestinal tract and of the chest were normal. Pancreatic calcification was noted.

Comment.—The patient was an unstable, nervous person. His diarrhea improved with rest and diet in the hospital. No specific therapy was used.

CASE 11.—An alcoholic, diabetic white man, 60 years of age, had no symptoms of pancreatic calcification. He is alive at the present writing.

History.—On Nov. 24, 1931 the patient had an appendectomy because of abdominal pain. The appendix was not inflamed, and there was no diabetes. He reentered the hospital later with acute and chronic alcoholism. On April 10, 1943 a hemorrhoidectomy was done. There was still no sign of diabetes. In 1947 complaints of polyuria, polydipsia, polyphagia, vertigo and ankle edema led to establishment of a diagnosis of diabetes. The family history was negative for diabetes.

Results of Physical Examination.—Retinal arteries revealed arteriosclerotic changes. The arteries displayed moderate arteriosclerotic disease. No pulse was palpable in the extremities.

Results of Laboratory Studies.—The blood sugar levels ranged from 80 to 300 mg. per 100 cc. The remainder of the blood chemical values were within the normal range. The reactions to the serologic tests were negative.

Roentgenologic Appearance.—Diffuse calcification of the pancreas was diagnosed roentgenographically. Films made after administration of a barium sulfate enema were normal.

Comment.—The patient's diabetes was controlled by diet, with daily administration of 20 units of protamine zinc insulin and 35 units of regular insulin.

CASE 12.—This case is presented in detail in the text.

CASE 13.—This alcoholic, tuberculous white man, 48 years of age, displayed symptoms of calcification of the pancreas but did not have diabetes. It is not known whether he is alive.

History.—The patient had a history of recurrent diarrhea for 16 years. Cough, chills, fever, hemoptysis, swelling of the abdomen and jaundice had occurred for 10 months. The mother had had diabetes.

Results of Physical Examination.—The upper lobe of the right lung showed cavitation. Fluid was present in the abdomen.

Results of Laboratory Studies.—A dextrose tolerance test revealed 68 mg. of sugar on fasting, 118 mg. at one-half hour, 164 mg. at one hour, 105 mg. at two hours and 105 mg. at three hours. The urine specimens gave negative reactions for sugar. Benzoic acid, 0.35 Gm., was administered intravenously. The icterus index was 4 and the thymol turbidity 6.4 units. The prothrombin time was 48 per cent of normal. Albumin measured 3.74 Gm. and globulin 4.64 Gm. per 100 cc. Cephalin flocculation was 4+.

Roentgenologic Appearance.—Pulmonary tuberculosis with cavitation and diffuse pancreatic calcification were noted on roentgenograms. The film made on administration of a barium sulfate enema was normal.

Comment.—The patient was treated for pulmonary tuberculosis with streptomycin. The pancreatic calcification caused the diarrhea. The patient had had a diagnosis of mucous colitis for 16 years.

CASE 14.—A Negro man, 42 years of age, had symptoms of diffuse calcification of the pancreas. He was not an alcoholic, nor did he have diabetes. He is alive at the present writing.

History.—The patient complained of gnawing epigastric pain for two years occurring one hour after meals and relieved by ingestion of food. Relief was also obtained by the taking of antacids. There was a 20 pound (9.1 Kg.) loss in weight. The patient had no constipation, diarrhea or jaundice. Scrofula had occurred at the age of 14 years.

Results of Physical Examination.—Physical examination showed an essentially normal condition.

Results of Laboratory Studies.—Laboratory studies were incomplete. Gastroscopy disclosed a normal appearance.

Roentgenologic Appearance.—Study of the gastrointestinal tract and colon revealed no abnormalities. Multiple calculi were seen in the pancreas. The roentgenogram of the chest showed old calcified lymph nodes in the right and left hili and calcified deposits in the apex of the left lung.

Comment.—The patient had typical ulcer symptoms without relief from treatment with an ulcer regimen.

CASE 15.—A diabetic, tuberculous, alcoholic Negro man, 52 years of age, displayed symptoms of calcification of the pancreas. Autopsy observations are noted in the section on pathological material.

History.—There had been repeated episodes of pain in the left upper abdominal quadrant and left flank, lasting 12 to 24 hours, since 1941. The gallbladder and appendix were removed in 1942. The present admission (1948) was for far advanced pulmonary tuberculosis, resulting in death.

Results of Physical Examination.—The patient weighed 97 pounds (44 Kg.). The chest expansion was limited. Post-tussive rales were heard in the apexes of both lungs.

Results of Laboratory Studies.—A dextrose tolerance test done on Feb. 25, 1947 showed 123 mg. of sugar on fasting, 232 mg. at one-half hour, 232 mg. at one hour, 336 mg. at two hours and 294 mg. at three hours. The urine specimens taken at one, two and three hours all showed a 1 + reaction for sugar.

Roentgenologic Appearance.—Roentgenograms disclosed diffuse calcification of the pancreas. A roentgenogram of the chest in 1942 was negative for tuberculosis, but one in 1948 showed far advanced pulmonary tuberculosis.

Comment.—The patient had hypogastric pain and was suspected of having an obstruction of the bowel on several occasions. At the time of removal of the gallbladder and appendix in 1942, the calcification of the pancreas was discovered.

CASE 16.—An alcoholic, diabetic white man 51 years of age, had symptoms of calcification of the pancreas. He is alive at present.

History.—The patient lost 50 pounds (22.7 Kg.) in weight in eight months. He complained of pain in the right upper abdominal quadrant which radiated about the torso and shot down both legs. He described the pain as a "constant ache" exaggerated by eating and causing sleeplessness. At times the pain radiated under the left scapula.

Results of Physical Examination.—The patient was a thin, chronically ill white man, with a blood pressure of 152/112 and hyperesthesia over the left thoracic region, especially over the lower two ribs on the left. The knee jerks and the Achilles jerks were absent. Examination elicited marked tenderness in the calves. Gastroscopic examination revealed nothing abnormal.

Results of Laboratory Studies.—Examination of the stool on six occasions showed no abnormality. The results of the liver function tests were normal. The blood sugar level ranged from 74 to 205 mg. per 100 cc. The studies with ingestion of a piece of thymus were unsuccessful.

Roentgenologic Appearance.—The gallbladder, lumbar portion of the spine, chest, kidneys, ureters, bladder and gastrointestinal tract were normal. The only abnormality was calcification in the pancreas.

Comment.—The patient gained 20 pounds while in the hospital. The abdominal pain remained unchanged; nevertheless, surgical intervention was not considered. The diabetes was controlled with the daily use of 14 units of protamine zinc insulin and 28 units of regular insulin.

CASE 17.—A 50 year old white man had no symptoms of diabetes or of calcification of the pancreas. He was not an alcoholic. Autopsy observations are presented in the section on pathological material.

History.—The patient had been acutely ill for four weeks with cough and malaise. The past history revealed no abdominal distress.

Results of Physical Examination.—Examination revealed pneumonia in the right lung. Fibrillation of the heart, with a pulse rate of 158, was noted. The edge of the liver was palpated 3 fingerbreadths below the costal margin. The left leg was swollen.

Results of Laboratory Studies.—There were 2,400,000 red blood cells and 39,200 white blood cells. The urine gave no reaction for sugar, and microscopic examination showed no abnormality.

Roentgenologic Appearance.—Roentgenograms revealed bronchopneumonia.

Comment.—The patient collapsed and died four days later. At postmortem examination a calcified pancreas was observed.

CASE 18.—This case is described in detail in the text.

CASE 19.—A diabetic, alcoholic white man, 62 years of age, had symptoms of calcification of the pancreas. He is alive at the present writing.

History.—This patient first entered the hospital on June 15, 1944. He had a history of pancreatitis with partial removal of the pancreas and gallbladder in 1929. There were repeated admissions for chronic alcoholism and recurrent pain in the upper abdomen with loose white stools. The presence of a salivary calculus was recorded in 1948.

Results of Physical Examination.—The patient was obese. The liver edge was palpable 3 fingerbreadths below the costal margin.

Results of Laboratory Studies.—Studies done in 1948 revealed a serum amylase level of 72 mg. per 100 cc. The feces showed the presence of a few meat fibers and no fat. A dextrose tolerance test on April 11, 1948 showed 176 mg. on fasting, 234 mg. at one-half hour, 326 mg. at one hour, 374 mg. at two hours and 232 mg. at three hours. The urine specimen showed a 1 + reaction for sugar. In 1950 serum amylase measured 23 mg. on admission. On the day after admission serum amylase was 13.2 mg. per 100 cc., and 10 days after admission the value was 51 mg.

Roentgenologic Appearance.—Roentgenograms showed calcification of the pancreas.

Comment.—Up to 1948 the patient's diabetes was controlled with diet alone. In 1950 after the last episode 8 units of insulin was needed daily. Pain was continuous in the epigastric region and radiated into both flanks.

CASE 20.—A diabetic, alcoholic white man, 39 years of age, had symptoms of pancreatic calcification. He is alive at the present writing.

History.—The first episode of epigastric pain occurred in 1947 and was treated as an ulcer. The patient complained of anorexia and some vomiting and was advised to discontinue drinking. The pain persisted as a deep ache in the epigastrium running through to the back. Initially he had relief from ingestion of milk, but at present the pain is constant and is aggravated by the drinking of alcohol. The patient has had six to eight fatty stools daily for the past several years. In the past two years the loss of weight has been 25 pounds. The initial diagnosis was peptic ulcer.

Results of Physical Examination.—The patient was a well developed, well nourished man with epigastric tenderness. No abnormalities were noted.

Results of Laboratory Studies.—Studies in 1950 showed 205 mg. of serum amylase. This value dropped to 92 mg. after seven days. The feces presented a peanut butter appearance. The hemogram was normal. The sedimentation rate was 63 mm. The results of liver function tests were normal, as were the results of gastric analysis. A dextrose tolerance test revealed 104 mg. of sugar on fasting, 224 mg. at one-half hour, 262 mg. at 1 hour, 206 mg. at two hours and 97 mg. at three hours. The first two urine specimens contained no sugar, the one hour and two hour specimens each showed a 4 + reaction and the three hour specimen contained but a trace of sugar.

Roentgenologic Appearance.—A roentgenogram of the colon revealed a few diverticula. Study of the gallbladder showed it to be nonfunctioning. A gastrointestinal series disclosed widening of the duodenal loop and diffuse calcification of the pancreas.

Comment.—Gastroscopy revealed hypertrophic gastritis. The patient's diabetes was controlled with diet.

CASE 21.—This alcoholic, diabetic white man, 56 years of age, showed symptoms of calcification of the pancreas. Autopsy observations are presented in the section on pathological material.

History.—The first episode of epigastric pain occurred in 1945 and was localized to the midabdomen, with radiation to the twelfth dorsal vertebra laterally to both sides. The pain was located deep within the body and was dull in character, increasing in intensity from the time of its onset and later remaining constant. The patient complained of vomiting but had no stool disturbances. The presence of diabetes was established in February 1946 with a positive dextrose tolerance curve. The stools were peanut-butter-like.

Results of Physical Examination.—The patient was a well nourished man having definite tenderness in the epigastrium, with no rigidity and no palpable masses.

Results of Laboratory Studies.—The serum amylase measured 123 mg. per 100 cc. and dropped to 10 mg. after subsidence of symptoms. The dextrose tolerance test showed 111 mg. of sugar on fasting, 202 mg. at one hour, 166 mg. at two hours, 122 mg. at three hours and 91.7 mg. at four hours. The one hour and two hour urine specimens each gave a 4 + reaction for sugar. Other specimens contained no sugar.

Roentgenologic Appearance.—Roentgenograms of the abdomen in 1947 were questionable for the presence of pancreatic calculi. Definite evidence of the condition was found in 1948.

Comment.—The diabetes was controlled with a diet containing 215 Gm. of carbohydrate, 100 Gm. of protein and 115 Gm. of fat and with daily administration of 32 units of insulin. A cholecystectomy was performed in 1947, but the gallbladder was seen to be only slightly thickened. The patient continued to have recurrent epigastric pain.

Case Reports

MALIGNANT TUMORS OF THE DUODENUM

Report of Two Cases

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THE RARITY of primary carcinoma of the duodenum has long been emphasized. Like the fallopian tubes and spleen, this viscus enjoys only a relative immunity from involvement with primary carcinoma. The more recent studies [1] suggest a higher incidence than is generally realized. In a combined series [1f] numbering 483,695 autopsies, primary carcinoma of the duodenum was found to be present in 0.035 per cent. Three per cent of all carcinoma occurs in the small intestine, and of this number about half are found in the duodenum (45.6 per cent). To date 483 well documented cases of primary carcinoma of the duodenum have been recorded.[1f] This figure represents a well screened series in that the not infrequent vaterian and pancreatic carcinoma which so commonly mimic duodenal carcinoma have been carefully excluded.

Sarcoma of the duodenum is extremely rare, its incidence being about 0.003 per cent, or one-tenth that of primary carcinoma.[2] The recorded cases to date number well under 100. In contrast to carcinoma of the duodenum, it occurs oftenest in young persons. The sex distribution is equal for both types of malignant growth.

It is our purpose to present two cases of malignant tumors of the duodenum, one of which was diagnosed preoperatively.

CASE HISTORIES

CASE 1.—K. D., a 55 year old German-born white woman, was first admitted to Grasslands Hospital in May 1949 for intractable diarrhea. The stools were profuse and associated with moderately severe, generalized abdominal cramps. On occasion she noted several episodes of black stools.

Physical examination revealed a well developed, rather well nourished, pale white woman. Her temperature was 98.6 F. (rectum), the pulse rate 88 and regular and the blood pressure 120/60. There were no abnormal findings throughout the remainder of the physical examination.

From the Divisions of Internal Medicine and Surgery, Grasslands Hospital.

1. (*a*) Hoffman, W. J., and Pack, G. T.: Cancer of the Duodenum, Arch. Surg. **35**:11-63 (July) 1937. (*b*) Stewart, H. L., and Lieber, M. M.: Carcinoma of the Suprapapillary Portion of the Duodenum, ibid. **35**:99-129 (July) 1937. (*c*) Lieber, M. M.; Stewart, H. L., and Lund, H.: Carcinoma of the Infrapapillary Portion of the Duodenum, ibid. **35**:268-289 (Aug.) 1937. (*d*) Howard, J. H.: Carcinoma of the Duodenum, Am. J. M. Sc. **206**:735-746 (Dec.) 1943. (*e*) Dixon, C. F.; Lichtman, A. L.; Weber, H. M., and McDonald, J. R.: Malignant Lesions of the Duodenum, Surg., Gynec. & Obst. **83**:83-93 (July) 1946. (*f*) Kleinerman, J.; Yardumian, K., and Tamaki, H. T.: Primary Carcinoma of Duodenum, Ann. Int. Med. **32**:451-465 (March) 1950.

2. Feldman, M.: Clinical Roentgenology of the Digestive Tract, Baltimore, William Wood & Company, 1938.

The blood count on admission revealed 2,470,000 red blood cells, 4.5 Gm. of hemoglobin and 4,250 white blood cells, with a normal differential count. The hematocrit was 16 per cent. Gastric analysis failed to reveal any free hydrochloric acid after administration of histamine.

The patient was given a transfusion soon after admission. The hematocrit reading rose to 31 per cent, the red blood cell count to 3,283,000 and the hemoglobin concentration to 8 Gm.

A roentgenogram of the gastrointestinal tract showed an evanescent hiatus hernia which was small and self reducing. Tenderness was elicited over the duodenum, and it was reported that the second portion of the duodenum was somewhat distended. It was felt that the patient was bleeding from the hiatus hernia rather than from a duodenal lesion, and she was discharged from the hospital with that diagnosis.

Two days after discharge, the patient experienced a severe bout of hematemesis and was readmitted for surgical intervention. She received whole blood transfusions. An exploratory

Fig. 1 (case 1).—Photomicrograph showing leiomyosarcoma.

laparotomy was performed on July 8. A large, firm, round mass 7 cm. in diameter was palpated behind the second portion of the duodenum. Along with this mass, a part of the stomach was removed. The common bile duct was inserted into the jejunum; gastrojejunostomy and pancreaticojejunostomy were performed.

Follow-up examinations in our outpatient department have revealed some improvement in her general condition, and serial roentgenograms of the gastrointestinal tract showed a well functioning gastrojejunostomy opening.

Laboratory Report.—The specimen consisted of a 10 cm. segment of duodenum. Attached to the proximal portion was a 5 cm. segment of the pyloric end of the stomach. In the second portion of the duodenum was a tumor which had been cut across at its distal end. The tumor presented itself on the external surface of the duodenum as a soft, hemorrhagic mass measuring 5 by 7 by 10 cm. On opening the duodenum, this mass was seen to have ulcerated the mucosa for a distance of about 5 cm.; the mass was friable, necrotic and hemorrhagic and partially occluded the lumen. Several enlarged, firm lymph nodes were observed on the concave aspect

of the duodenal loop. The common duct could not be identified in the specimen. The portion of stomach received appeared normal. Histological examination of the tumor revealed sheets of spindle-shaped cells with oval and round vesicular nuclei. In places the cells were lined up in rows around the penetrating blood vessels. The tumor appeared to arise in the muscular coat of the duodenum with secondary penetration of the mucosa. There were a few areas of interstitial hemorrhage and several large areas of necrosis. Some of the vessels in the tumor were surrounded by a mononuclear cell infiltrate. Masson's tetrachrome stain revealed only a few collagenous fibers in the tumor. The lymph nodes were completely replaced by tumor that

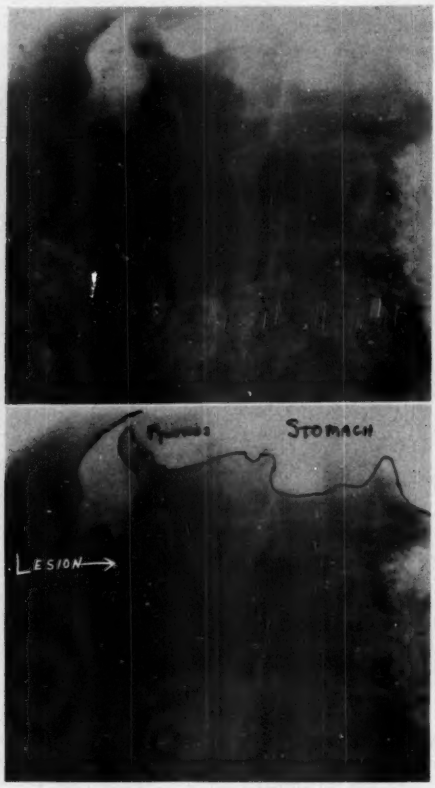

Fig. 2 (case 2).—Upper, appearance of the barium sulfate contrast study of the duodenal area. Lower, contrast study of the duodenal area.

resembled the primary tumor mass. The diagnosis was leiomyosarcoma of the duodenum and secondary leiomyosarcoma in regional lymph nodes (see fig. 1).

Case 2.—E. S., a 51 year old white Danish housewife, was first seen in our outpatient department in November 1949 with presenting complaints of gastric distress, some pain in the midepigastrium following meals and severe episodes of vomiting in the past few weeks.

Her pain was described as dull in character and was limited to the epigastrium. She noted a weight loss of approximately 12 pounds (5.4 Kg.) during the two months prior to entry. Only rarely did ingestion of food relieve her abdominal distress, but in the recent past, vomiting

seemed to give some relief. A gastrointestinal series done in the outpatient department showed a constant filling defect in the second portion of the duodenum. There was no obstruction to the flow of barium sulfate solution, but irregularity and narrowing of the lumen were noted just proximal and distal to the constant filling defect (see figs. 2, 3 and 4). The members of the x-ray department considered the most likely explanation to be neoplasm of the duodenum.

She was admitted for surgical treatment on December 15. Physical examination revealed a well developed, well nourished white woman. The blood pressure was 128/88, the pulse rate 84 and the respiratory rate 18. The results on general physical examination were essentially within normal limits save for a moderate tenderness in the midepigastrium. The blood count

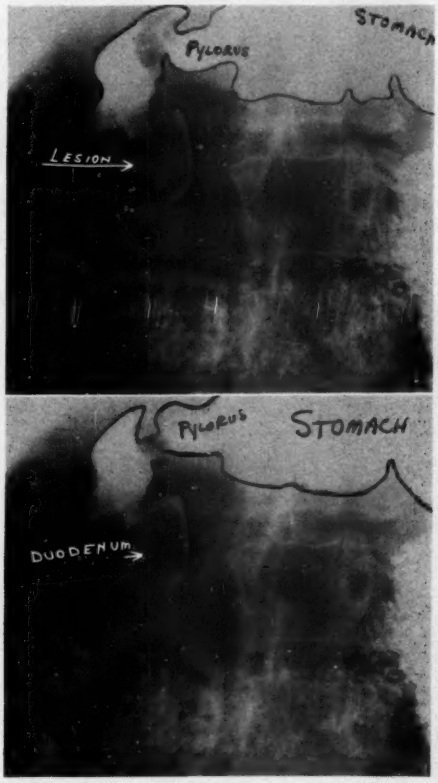

Fig. 3 (case 2).—Upper, spot film of the contrast study. Lower, roentgenographic appearance of the duodenal area.

was 4,007,000 red blood cells, 8.5 Gm. of hemoglobin, 19,150 white blood cells and a hematocrit reading of 31 per cent.

The patient was prepared for operation, and on December 28 a modified Whipple procedure (excision of ampulla of Vater) was performed, including partial resection of the stomach, resection of the duodenum, partial pancreatectomy, pancreaticojejunostomy and choledochojejunostomy. The patient experienced a moderately stormy period following these extensive surgical measures, receiving a total of 3,000 cc. of whole blood in the immediate postoperative period. Her blood count was maintained at about 5,000,000 red blood cells, with a hemoglobin content of 12.5 Gm. She was discharged improved on Feb. 8, 1950.

In March 1950 she was readmitted because of gastroenteritis. The disorder responded well to conservative treatment, and she was discharged in good condition. One month later a revisit to the outpatient department disclosed the presence of a group of hard lymph nodes in

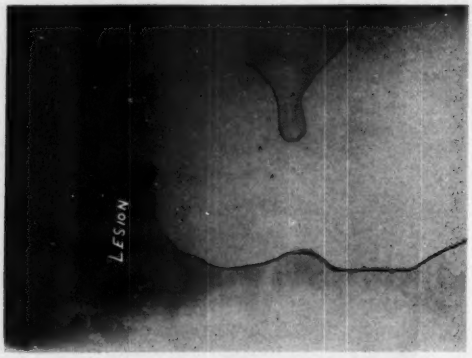

Fig. 4 (case 2).—Barium sulfate study of the stomach and duodenum.

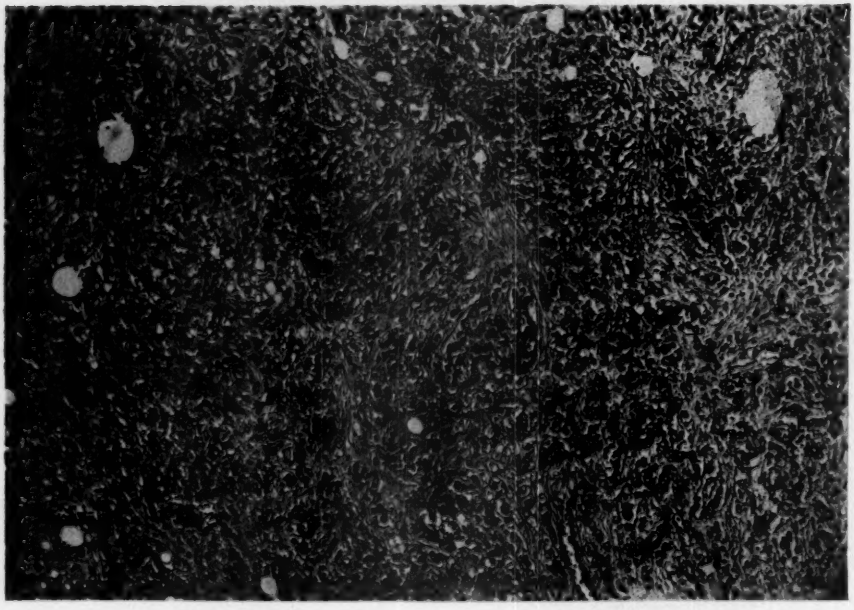

Fig. 5 (case 2).—Photomicrograph showing adenocarcinoma.

the left supraclavicular area. Biopsy of one of these revealed adenocarcinoma. Her general condition was noted to be somewhat poorer after her discharge from the hospital.

Laboratory Report.—The specimen consisted of the duodenum, a 3 cm. portion of attached stomach and the head and body of the pancreas. In the first and second portions of the

duodenum, almost 4 cm. from the pylorus, was a constricting annular tumor 5 cm. long. The edge of the tumor was raised and the central portion ulcerated. Tumor had infiltrated to the serosa. The common duct passed along the posteromedial surface of the tumor and was compressed by it but not grossly invaded; the duct opened into the duodenum about 1 cm. below the tumor. There was no lesion demonstrable at the ampulla of Vater. At one point the pancreas was invaded by the tumor to a depth of about 2 cm. The pancreatic duct was slightly dilated throughout and completely obstructed by tumor 2 cm. from the ampulla. Just above the midportion of the excised pancreas was an enlarged, firm lymph node measuring 2 cm. in diameter. Histological examination revealed sheets and cords of dark basophilic cells, in some places forming distinct glands. The nuclei were hyperchromatic, and many were undergoing mitosis. There were a few patchy areas of necrosis. Sections of the pancreatic duct showed complete occlusion by tumor tissue. The outer layers of the common duct were infiltrated by tumor, but the lumen and epithelium were intact. The pancreas distal to the tumor was within normal limits. The lamina propria of the stomach was infiltrated by a few polymorphonuclear leukocytes. The peripancreatic lymph nodes were completely replaced by tumor tissue. The diagnosis was adenocarcinoma of the duodenum and secondary carcinoma in regional lymph nodes (fig. 5).

COMMENT

Etiological Factors.—It would profit little to discuss all the etiological implications of this disease. This has been excellently done by Hoffman and Pack [1a] and Dixon.[1e] The consensus is that no one theory is applicable to all cases. It is generally believed that malignant tumors of the duodenum originate from anaplastic changes in the duodenal mucosa. Indeed, it seems a paradox that the area of the intestine most subject to both physical and chemical irritation should be least affected.

Pathological Aspects.—Both carcinoma and sarcoma of the duodenum occur as polypoid or infiltrative growths. Carcinoma characteristically produces stenotic lesions with dilatation proximal to the obstruction, while sarcoma encroaches on the lumen only to a small degree, insufficient to cause obstruction. Ulceration occurs in both, leading to hemorrhage. Metastasis usually occurs late in the disease and involves the regional lymph nodes, liver, pancreas and lungs.

Symptoms.—The early history of malignant tumors of the duodenum frequently consists of a group of vague prodromal symptoms. These symptoms are commonly referable to the stomach, gallbladder and pancreas since, during the early infiltrative phase of the disease, the physiological state of the duodenum is little impaired. On less frequent occasions a dramatic onset is seen, characterized by hematemesis, syncope and, rarely, exsanguinating hemorrhage.

The commonest complaints in this latent period are vague epigastric fulness, upper abdominal pain, anorexia, nausea, vomiting and gaseous eructations. Weakness and anemia may likewise be present, the latter most usually resulting from blood loss.

Pain is a common symptom and is variable in both character and location. It follows no pattern suggestive of its origin.

The latent period may be of several weeks to many months' duration. The inevitable changes in the extent and morphological character of the lesion soon lead to an altered local physiological condition. This results in certain gradual and oftentimes sudden and dramatic changes in symptoms which, in some measure, are modified by the location and consistency of the lesion and may be classified into four distinctive groups.

1. Obstruction: The symptoms are referable to the stomach and consist in the main of an intensification of the preexisting nausea, anorexia, epigastric fulness and pain observed in the latent phase. As the obstruction progresses, the symptoms increase further in their severity and colicky, intense epigastric pain and vomiting become prominent. With the advent of vomiting dehydration, weight loss, weakness, constipation and toxemia soon supervene, to be followed shortly by shock, uremia and tetany.

2. Penetration and Perforation: The symptoms of this group differ little from those present in cases of malignant tumors of the pancreas or chronic pancreatitis.

3. Ulceration and Hemorrhage: Anemia and weakness are common symptoms resulting from ulceration and sloughing off of part of the lesion. Hemorrhage is manifested by hematemesis, melena or frank blood in the stool. Bleeding may be gradual or brisk, leading to varying degrees of anemia. On rare occasions exsanguinating hemorrhage may be the presenting symptom of the disease. The anemia is most frequently observed to be of the microcytic, hypochromic variety and almost always results from blood loss. In Dixon's series [1e] blood loss was demonstrated in all cases in which anemia was found to be present. The occasional case of normochromic, macrocytic anemia encountered in this disease has been explained by some authors on the basis of diminished productivity of specific antianemic factor elaborated by Brunner's glands in the duodenum. It is worthy of note in this regard that hemopoiesis is not altered by total duodenectomy and partial gastrectomy.[1e]

4. Jaundice: Jaundice is usually a late symptom and may result from (*a*) encroachment on the biliary excretory system through pressure on the common duct or obstruction of the papilla of Vater or (*b*) metastasis to the liver, which is an infrequent occurrence and then only in the terminal stages of the disease.

From this it will be seen that the presence of jaundice does not necessarily imply a lesion of the periampullary portion of the duodenum. Extension from lesions in the supra-ampullary and infra-ampullary portions of the duodenum, edema in the area of the ampulla, pressure from adjacent involved lymph nodes or liver metastasis may be the factor responsible.

Early onset of jaundice, however, suggests periampullary involvement, particularly in the absence of signs of duodenal obstruction. Intermittent jaundice implies a duodenal lesion, though one cannot distinguish between vaterian and extravaterian involvement.

The physical signs and laboratory findings of the patient with a malignant lesion of the duodenum vary with the duration and extent of the disease and are, in a great measure, modified by its complications. Thus, intestinal obstruction, biliary duct obstruction and hemorrhage each lead to highly individualized pathophysiological states with characteristic clinical patterns of signs and symptoms. Weight loss and melena appear as common findings in almost all cases. A palpable mass was noted by Hoffman and Pack [1a] in 55.5 per cent of a series of 18 cases. Results of laboratory investigation other than roentgen examination are not diagnostic. Study of the cytological characteristics of the duodenal contents is as yet to be established as a reliable diagnostic medium.

Roentgenologic Diagnosis.—The early literature fails to stress the value of roentgenograms in diagnosis of primary neoplasm of the duodenum. This may possibly be ascribed to the inefficiency of the technics then in use and to a lower index of sus-

picion on the part of the roentgenologist. In the past two decades roentgenography has played an increasingly important role in diagnosis. Feldman [2] stated that "the roentgen method of examination offers the only means by which a pre-operative diagnosis can be made."

Patients presenting themselves early in the disease may fail to exhibit any roentgenographic evidence whatsoever. But since most patients are seen with moderately advanced or late lesions roentgenologic investigation is usually productive. In a combined series [3] of 31 cases the existence of duodenal invasion or obstruction was noted, but a precise diagnosis of carcinoma of the duodenum was made only in one instance.

The changes seen on roentgenologic examination vary with the character, location and extent of the lesion. In regard to the supra-ampullary lesion confusion will exist because of a duodenal deformity which is indistinguishable from that of an ulcer. Loss of mucosal pattern and thickening and fixation of the wall are frequently observed. As the lesion enlarges and ulcerates, filling defects and craters become visible. With the advent of stenosis, a not infrequent occurrence in this disease, characteristic roentgenologic signs of obstructed hollow viscus supervene. The stomach soon dilates, and evidence of six to 48 hour retention results.

Diagnosis.—The diagnosis of malignant tumor of the duodenum is infrequently entertained owing to the rarity of the lesion and the difficulties attending the analysis of the presenting symptoms and signs. The early stages of the disease present so few suggestive symptoms that diagnosis is well nigh imposible. With the progression of the lesion and the development of intermittent intestinal obstruction, it is important to determine the level at which obstruction exists. This can best be done by roentgenologic investigation. In the last analysis the roentgen examination serves as the key piece in the diagnostic jigsaw pattern. Without it diagnosis of this condition would, at best, be presumptive.

Treatment.—As metastasis is a late feature of this disease, surgical intervention should be considered in all cases. The Whipple procedures described for treatment of vaterian lesions are those generally employed. Preoperative measures are of vital importance in restoring the patient to an approximately physiological status. The disturbed physiological condition of intestinal obstruction with its implied dehydration, toxemia and electrolytic imbalance must be suitably corrected. Jaundice with its attendant effects on liver function creates a possible need for administration of vitamin K, glycogen and protein. Anemia and hypoproteinemia require correction by transfusion.

The immediate operative mortality in a recent series of 37 cases [1e] was 22 per cent. The outlook for long term survival, however, is poor, only one patient in the above series living six years following surgical treatment.

SUMMARY

One case of carcinoma and one case of leiomyosarcoma primary to the duodenum are presented. Both of these tumors were in middle-aged women; both underwent surgical treatment, and both are surviving after eight and 15 months, respectively. One case was tentatively diagnosed preoperatively by roentgenographic study. The importance of this lesion in differential diagnosis is emphasized.

3. Dixon and others.[1e] Weber, H. M., and Kirklin, B. R.: Roentgenologic Manifestations of Tumors of Small Intestine, Am. J. Roentgenol. **47**:243-253 (Feb.) 1942.

GAUCHER'S DISEASE WITH MEGALOBLASTIC BONE MARROW

Response to Therapy

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THE DIAGNOSIS of Gaucher's disease (lipid histiocytosis of kerasin type) is made on the basis of the following typical findings: hepatosplenomegaly, wedge-shaped pingueculae in the conjunctivas, pigmentation on the lower part of the legs, bone lesions which tend to occur in the head, neck and lower end of the femurs and a normal blood cholesterol level. Most usually there are hypochromic anemia, leukopenia and thrombocytopenia. The diagnosis is made conclusive by demonstration of typical Gaucher cells, and this is easily done by sternal marrow aspiration.[1]

Potter and McRae described a case of Gaucher's disease treated with liver extract.[2] Their patient was admitted with hypochromic anemia. No bone marrow studies were made. Because of macrocytosis, the patient received 3 to 4 vials of liver extract daily for 11 months. There was symptomatic improvement, and a decrease in skin pigmentation, pingueculae and spleen size occurred. The erythrocyte count returned to normal, and the hemoglobin concentration rose, but it never went above 66 per cent (Sahli). Although this patient did not have true hypochromic macrocytic anemia, on the basis of this report other investigators treated a patient having Gaucher's disease with liver extract.[3] They observed only temporary hematological improvement. However, a high vitamin, high caloric diet and iron therapy were also given, making it difficult to assess the true value of the liver extract therapy.

We believe that the following case represents the first report of Gaucher's disease associated with megaloblastic anemia in which specific antianemic therapy was successful.

Read before the Society for the Study of Blood at the New York Academy of Medicine, May 23, 1950.

From the Third (New York University) Medical Service (Dr. Milton B. Rosenbluth, Director), Goldwater Memorial Hospital, Welfare Island.

1. Groen, J., and Garrer, A. H.: Adult Gaucher's Disease, with Special Reference to the Variations in Its Clinical Course and the Value of Sternal Puncture as an Aid to Its Diagnosis, Blood **3**:1221-1237, 1948.

2. Potter, E. B., and McRae, C. C.: Gaucher's Disease: Report of Two Cases, with a Remission in One Following Administration of Liver Extract, Am. J. M. Sc. **185**:92-96, 1933.

3. Mandelbaum, H.; Berger, L., and Lederer, M.: Gaucher's Disease: I. A Case with Hemolytic Anemia and Marked Thrombopenia; Improvement After Removal of Spleen Weighing 6,822 Grams, Ann. Int. Med. **16**:438-446, 1942.

REPORT OF CASE

G. M., a 48 year old Jewish man, was treated in 1921 for congenital syphilis at the Presbyterian Hospital, New York. He received three courses of antisyphilitic therapy. Results of physical examination were normal. Since 1922, he was followed at the Neurological Institute in New York city for petit mal with occasional grand mal seizures. At this time his liver was palpable 9 fingerbreadths and the spleen 11 fingerbreadths below the costal margin. In 1938 he was readmitted to Presbyterian Hospital with clinical scurvy due to an antiepileptic fish diet. A history of fulness of the left upper abdominal quadrant since childhood was elicited. A diagnosis of Gaucher's disease was made on the basis of the sternal marrow findings and roentgenograms of the femurs. His epilepsy was fairly well controlled with the use of phenobarbital. A psychiatric examination revealed him to be a paranoid schizophrenic with borderline mental deficiency. Except for infrequent attacks of epilepsy, the patient felt well until January 1949. During this time he managed to work as a dental assistant.

Six months before the present admission (June 1949) to Presbyterian Hospital, he first noted the onset of anorexia, progressive weakness, fatigability, exertional dyspnea, orthopnea and ankle edema which was most troublesome in the morning. His diet was restricted to fresh fruit and vegetables. There was a resulting weight loss from 168 to 157 pounds (76 to 71 Kg.). He also noticed decreasing visual acuity with blurring. For two months he had dull aching pains in both legs from the ankles to above the knees while walking.

His family history revealed that one brother died at the age of 28 with classic Gaucher's disease and lung abscess. Three other siblings and the parents had no known Gaucher's disease.

The patient was again admitted to the Presbyterian Hospital in June 1949 with a temperature of 101.2 F., a pulse rate of 98, a respiration rate of 16 and a blood pressure of 104/48. He was a cachectic white man with protuberant abdomen who appeared acutely ill. Physical examination revealed retinopathy with small white exudates and old and fresh hemorrhages in both fundi. The mouth showed gingival hypertrophy and poor dental hygiene. The veins of the neck were distended and filled from above. There was no glandular enlargement. The thorax was funnel shaped. There were dulness and decreased breath sounds at the base of the right lung, with slightly decreased breath sounds and a few scattered rales in the right side of the chest posteriorly. The heart was slightly enlarged to the left. There was a loud apical systolic murmur. The pulmonary second sound was louder than the aortic second sound. The rhythm was regular. The liver edge was 5 fingerbreadths below the costal margin and acutely tender to palpation. The spleen was hard and tender and extended down to within 2 cm. of the left inguinal ligament. Marked pitting edema over both legs and moderate edema over the sacrum were noted. Neurological examination showed a slight decrease in vibratory sense in both legs, but results otherwise were normal.

Laboratory Data.—There were 5.0 Gm. of hemoglobin per 100 cc. and 1,450,000 erythrocytes and 1,500 leukocytes per cubic millimeter, with a differential count of 61 per cent neutrophils, 35 per cent lymphocytes and 4 per cent monocytes. Reticulocytes were 1.7 per cent and thrombocytes (platelets) 56,000 per cubic millimeter. Urinalysis showed no abnormality; the reaction for urobilinogen was positive in a dilution of 1:20. The erythrocyte sedimentation rate was 5 mm. per hour. The hematocrit reading was 14.8 per cent and the erythrocyte mean corpuscular volume 100 cubic microns. The results of capillary fragility and erythrocyte fragility tests were normal. The Coombs test gave a negative reaction. Blood and urine cultures were negative for pathogens. Other reports were as follows: The stool guaiac and Mazzini tests gave negative results. Alkaline phosphatase measured 1.7 Bodansky units, blood urea nitrogen 14 mg., total cholesterol 61 mg. (free, 25 mg., and esterified, 36 mg.), protein 4.7 Gm. (3.1 Gm. of albumin and 1.6 Gm. of globulin), serum calcium 7.9 mg. and serum inorganic phosphorus 4.5 mg. per 100 cc. The prothrombin time was 18.8 seconds. The cephalin flocculation test gave a 3 + reaction. Gastric analysis showed free hydrochloric acid after histamine stimulation. Venous pressure was 180 mm. of water. An electrocardiogram revealed right bundle branch block, indicating myocardial fibrosis secondary to coronary sclerosis. A roentgenogram of the chest was interpreted as showing left and right ventricular enlargement and increased bronchovascular markings. Roentgenograms of both femurs showed characteristic widening of the lower portions, with narrowing of the cortical margins. A gastrointestinal series revealed delayed gastric emptying and hypomotility of the intestine. This was interpreted as due to edema. An iliac crest aspiration revealed Gaucher cells in small amounts with a high proportion of megaloblasts.

Course in Hospital.—The patient was digitalized and given four blood transfusions. There was a gradual improvement in his symptoms, with heavy diuresis and loss of 21 pounds (9.5 Kg.) in weight. On the basis of the megaloblastic marrow, parenteral liver therapy was initiated. The hemoglobin content rose from 6 to 8.5 Gm. in two weeks, although the maximal reticulocyte count was only 4 per cent. Iron and vitamin supplements were also given. The patient received diphenylhydantoin (dilantin®) sodium for his epilepsy. He was then transferred to Goldwater Memorial Hospital in July 1949 for prolonged care and rehabilitation.

In July a repeat bone marrow study showed Gaucher cells and 5.5 per cent megaloblasts. The patient's hematological picture improved during the next two months with no specific

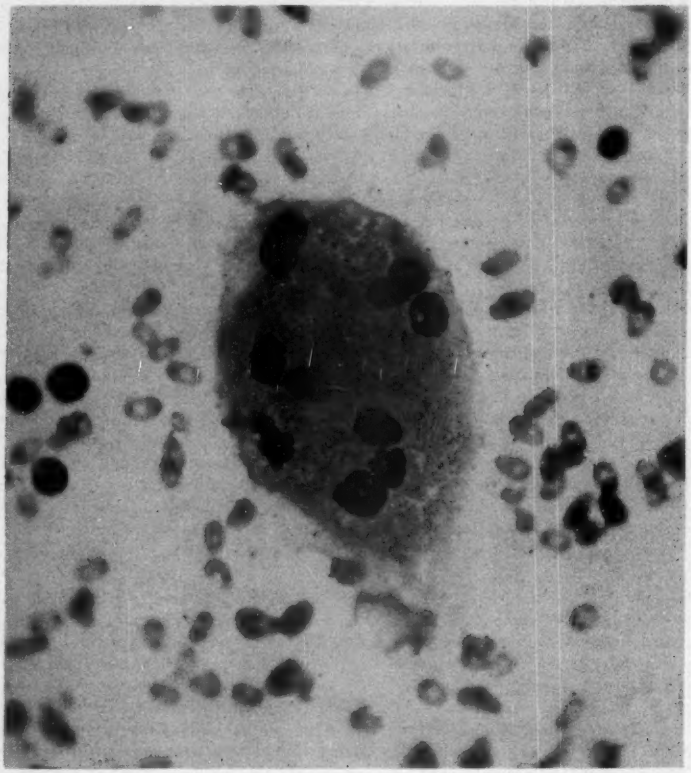

Fig. 1.—Sternal marrow of patient with Gaucher's disease before treatment demonstrating a multinucleated Gaucher cell.

therapy, so that by September 1949 the hemoglobin concentration was up to 10 Gm. per 100 cc., erythrocytes were 4,200,000 per cubic millimeter and hematocrit was 35 per cent. There was a persistent leukopenia, with the white cell count varying from 4,000 to 5,000 per cubic millimeter. Blood chemical studies showed an increase in albumin to 4.4 Gm., in calcium to 10.7 mg. and in cholesterol to 308 mg., with 32 per cent esters, per 100 cc. Cephalin flocculation was 2 + in 48 hours, and thymol turbidity was 11.8 units. Total bilirubin was 0.56 mg. per 100 cc. Other blood chemical values, the electrocardiogram and the appearance on roentgenologic examinations were essentially the same as at Presbyterian Hospital. Films of the humeri showed trabecular decalcification and destruction. A splenic puncture disclosed large collections of Gaucher cells.

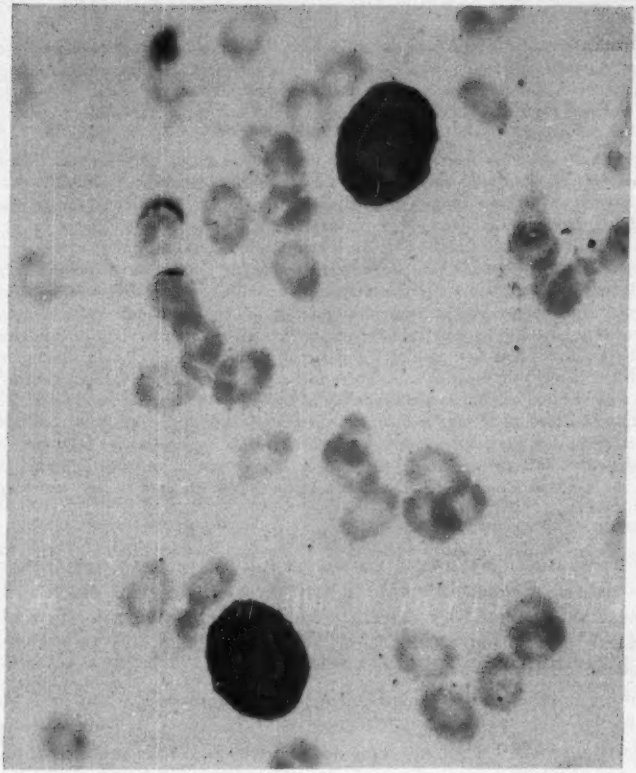

Fig. 2.—Another view of sternal marrow (fig. 1) demonstrating megaloblasts.

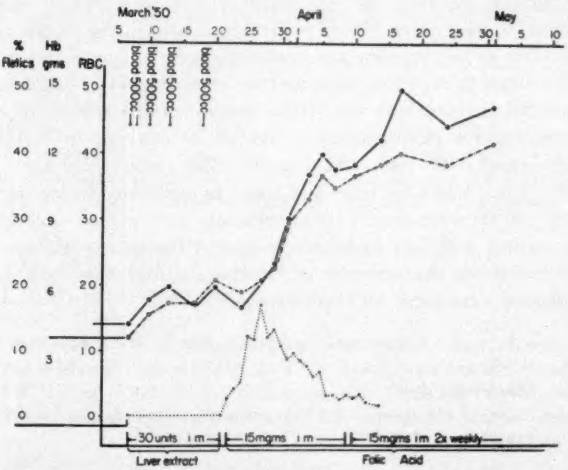

Fig. 3.—Hematological response to treatment with liver extract and folic acid in a patient with Gaucher's disease and megaloblastic anemia.

The patient's cardiac status was maintained for three months with administration of a salt-poor diet, digitalis and mercurials. There were no signs of cardiac decompensation other than 2 + ankle edema. To determine whether the failure had been due to anemia, the administration of the digitalis, mercurials and diet was stopped and the patient carefully watched. Cardiac failure did not recur.

During this period no specific antianemic therapy was given. In February 1950 his blood contained 4.0 Gm. of hemoglobin per 100 cc. and 1,410,000 erythrocytes and 950 leukocytes per cubic millimeter. The bone marrow showed Gaucher cells and 16.0 per cent megaloblasts (figs. 1 and 2). Treatment was started with large doses of liver extract (30 units daily), and the patient received 2,500 cc. of blood (fig. 3). There was no hematological response after 15 days. The possibilities of hypersplenism and acquired hemolytic anemia were considered because of the persistent pancytopenia. A Coombs test was done and gave a negative reaction. The reaction for urinary urobilinogen was positive in dilution of 1:100. The icterus index was 6. Because of failure of response to liver extract, the patient was given 15 mg. of folic acid intramuscularly daily. Reticulocytes rose to a peak of 17.0 per cent on the sixth day. At the same time the bone marrow had 1.5 per cent megaloblasts. There was a prompt rise in the hemoglobin concentration to 12.0 Gm. per 100 cc. and in the erythrocytes to 4,960,000 per cubic millimeter. The patient has been maintained on 15 mg. of folic acid given twice weekly by injection. Leukopenia, with the white cell count varying from 3,000 to 5,000 per cubic millimeter, has persisted. A dextrose tolerance curve was normal. A 48 hour stool fat determination revealed 5.73 Gm. At present the patient is completely asymptomatic. His appetite is excellent, and he feels better than at any time in the past.

COMMENT

The problem of erythrocyte maturation has not yet been completely resolved. Many cases of megaloblastic anemia have been reported that did not respond to treatment with potent liver extract.[4] Most of these were associated with pregnancy, the puerperium or the sprue syndrome. Folic acid produced excellent therapeutic effects in these.

However, cases of macrocytic anemia of undetermined origin have been unresponsive to folic acid therapy.[5] There are also some patients with pernicious anemia who relapsed while receiving adequate doses of folic acid and required liver extract to produce a remission.[6] It is evident that multiple factors may operate in the production of megaloblastic anemia.

In our patient the diagnosis of addisonian pernicious anemia was not entertained because of the finding of free hydrochloric acid in the gastric contents and the hypomotility of the intestine on roentgenography. The failure to respond to potent liver extract therapy also suggested the exclusion of this diagnosis. A nutritional macrocytic anemia was considered because of the history of limited diet, the presence of a low plasma albumin, the lack of response to liver therapy and the excellent result with folic acid therapy. The patient may have had a pure folic acid deficiency with a spruelike syndrome, as manifested by low serum calcium, hypomotility of the intestine, hypoproteinemia with edema and hyperchromic macrocytic anemia with free hydrochloric acid in the gastric contents. The persistence of leukopenia characteristic of Gaucher's disease may be a manifestation of hypersplenism associated with splenomegaly.

4. Davidson, L. S. P.: Refractory Megaloblastic Anemia, Blood **3**:107-120, 1948.

5. Adams, W. S., and Lawrence, J. S.: Folic Acid Therapy: Results of a Clinical Study, Am. J. M. Sc. **215**:487-497, 1948.

6. Hansen-Pruss, O. C.: Relapse of Patients with Pernicious Anemia Receiving Folic Acid, Am. J. M. Sc. **214**:465-468, 1947.

In recent years there have been reports showing the efficacy of folic acid in the treatment of macrocytic anemias.[7] The prerequisite for a beneficial response of the erythrocyte picture to folic acid therapy is megaloblastic arrest of the bone marrow.[5] There was also a case reported of a megaloblastic anemia with free gastric hydrochloric acid that did not respond to administration of either liver extract or vitamin B_{12} but did respond to treatment with folic acid.[8] Others have described patients with idiopathic steatorrhea, megaloblastic anemia and free gastric hydrochloric acid who did not respond to therapy with refined liver extracts.[9]

In man leukemic cells have a higher folic acid content than normal cells have.[10] However, it has not been proved that this necessarily reflects a greater folic acid requirement by the leukemic cell. Animal studies indicate that growing tissues of the normal organism vary significantly in their needs for folic acid.[11] This can be expected to hold for neoplastic tissues. It is, therefore, interesting to speculate that perhaps in our patient there may be an abnormal uptake of folic acid by the Gaucher cells, thus diverting it from its function in erythrocyte maturation. This postulation is not unreasonable since evidence has already been found that either pernicious anemia or a severe megaloblastic anemia may precede the onset of acute leukemia.[12] Leukemia with megaloblasts in the bone marrow and free gastric hydrochloric acid has also been reported.[13] It will be interesting to see whether the administration of folic acid will aggravate Gaucher's disease, as has been reported of leukemia.[14]

SUMMARY

A case of Gaucher's disease, with hyperchromic macrocytic anemia, megaloblastic bone marrow and free hydrochloric acid in the gastric juice, is presented. The condition failed to respond to large doses of potent liver extract. After folic acid therapy there was a return of the erythrocyte picture to normal values, with accompanying symptomatic improvement.

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9. Cooke, W. T.; Frazer, A. C.; Peenez, A. L. P.; Sammons, H. G., and Thompson, M. D.: Anomalies of the Intestinal Absorption of Fat: II. The Haematology of Idiopathic Steatorrhoea, Quart. J. Med. **17**:9-24, 1948.

10. Bethell, F. H., and Swendseid, M. E.: The Folic Acid Content of Leucocytes: Observations on Normal Subjects and Persons with Leukemia, abstracted, J. Clin. Investigation **25**:917-918, 1946.

11. Thiersch, J. B., and Philips, F. S.: Folic Acid and Antagonists in Neoplastic Disease, Am. J. M. Sc. **217**:575-585, 1949.

12. Collins, D. H., and Rose, W. M.: The Nature of Anaemia in Leukaemia, J. Path. & Bact. **60**:63-74, 1948.

13. Foy, H., and Kondi, A.: The Syndrome of Leukanaemia: Report of a Case, J. Path. & Bact. **58**:157-166, 1946.

14. Heinle, R. W., and Welch, A. D.: Experiments with Pteroylglutamic Acid and Pteroylglutamic Acid Deficiency in Human Leukemia, J. Clin. Investigation **27**:539, 1948.

Progress in Internal Medicine

SYPHILIS

A Review of the Recent Literature

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(Concluded from Page 322)

TREATMENT OF EARLY SYPHILIS

The appropriate treatment for early syphilis is slowly becoming apparent. Obviously, penicillin is the basis for all acceptable regimens, and, in spite of the successful five year follow-up study by Mahoney and his group [114] of the first four patients treated for syphilis with penicillin, there are still numerous complicating factors which have as yet prevented a standardized therapy for early syphilis. The trend toward ambulatory therapy has been discussed above. Observation on whether or not combined therapy is desirable have also been mentioned above and will be discussed further in certain reports, chiefly from abroad. Failures are being analyzed more fully than in previous years, and many of the new publications deal with this phase of the subject.

One of the basic tenets of syphilology is the dictum "Do not treat until a diagnosis has been established." In the modern trend this has been laid aside in favor of prediagnostic treatment of contacts of patients with infectious syphilis. Although such a procedure has merit, unless the amount of therapy is adequate those who have acquired the disease are undertreated and those who do not have it are overtreated. From the public health standpoint the eventual indications of the disease will, of course, require laying aside idealistic medical precepts in favor of practicality.

Diagnosis of Syphilis Confused by Penicillin Therapy of Other Diseases.—There is some confusion caused by the discovery of positive serologic reactions to the tests for syphilis in patients who have been given some penicillin just before the test reaction is reported. Sternberg and LeVan [115] selected case histories to illustrate the problems encountered in diagnosis and management. Although a diagnosis of biologic false positive reaction had to be considered in their cases, these authors note that even small amounts of penicillin may reduce the level of syphilitic reagin so that the diminishing titer is not diagnostic of a biologic false positive reaction. They recommend, therefore, the reduction in the number of such occurrences by including immediate routine serologic tests and the temporary withholding of penicillin therapy except when urgently needed.

114. Mahoney, J. F.; Arnold, R. C., and Harris, A.: Penicillin Treatment of Early Syphilis—First 4 Patients After 5 Years, J. Ven. Dis. Inform. **30**:350-355 (Dec.) 1949.

115. Sternberg, T. H., and LeVan, P.: The Diagnosis of Syphilis Confused by Penicillin Therapy of Other Diseases, Am. Pract. **3**:720-722 (Aug.) 1949.

Prediagnostic Treatment of Contacts with Infectious Syphilis.—Alexander, Schoch and Mantooth [116] report their experience with treatment during the incubation stage in 148 persons who were exposed to dark field–positive primary and secondary syphilis. In the past three years the authors have given abortive treatment, consisting of 900,000 units of calcium penicillin in oil and beeswax, 3 cc. of bismuth ethylcamphorate (and 0.05 to 0.06 Gm. of oxophenarsine hydrochloride) in one visit, to 256 persons. (The arsenical was omitted in the later part of this study.) Thirteen of these patients subsequently showed evidence of early syphilis. All evidence, clinical and epidemiological, and the response which these 13 patients showed to retreatment with abortive therapy support the diagnosis of reinfection. Of 161 persons (control group) who were in contact with patients with dark field–positive primary and secondary syphilis but who were not given abortive treatment, 100 (62.1 per cent) acquired early syphilis. The authors conclude that almost two thirds of normal persons exposed unprotected to infectious early syphilis acquire the disease; abortive treatment administered during the incubation stage affords almost 10 per cent protection. Oxophenarsine hydrochloride proved to be unnecessary in the abortive treatment schedule; abortive treatment should be considered mandatory in the management of persons who have been exposed to infectious syphilis. Preliminary observations with the use of calcium penicillin in oil and beeswax, bismuth ethylcamphorate and oxophenarsine (abortive treatment schedule) indicate results probably equal to those obtained with many penicillin schedules that have been systematically evaluated to date.

First Four Patients After Five Years.—Mahoney, Arnold and Harris [114] confirm the effectiveness of penicillin in the treatment of early syphilis in a six year follow-up study of the first four patient subjects discussed in their preliminary report of 1943. Each of the four patients had dark field–positive primary lesions at the time of therapy. Treatment consisted of amorphous penicillin administered intramuscularly in doses of 25,000 units every four hours, for a total of 48 injections or a total of 1,200,000 units. After therapy all patients showed negative serologic reactions within two to four months. One patient (case 4), however, had a dark field–positive lesion on the lip on the three hundred and third post-treatment day. Since this patient had 13 gonorrheal infections in the five years following initial treatment, it seemed that reinfection was the best possibility. Retreatment consisted of 2,400,000 units of penicillin every three hours for 60 injections. The patient's syphilis again became seronegative after the second course of therapy.

General Results of Penicillin Therapy.—Bauer and his co-workers [117] report the results of 45 schedules of penicillin therapy in early syphilis. The schedules utilized aqueous penicillin and penicillin in oil and beeswax alone or in conjunction with heavy metals. The data were obtained from rapid treatment centers throughout the country, which have been reporting to the Statistical Section of the Division of Venereal Disease, United States Public Health Service. The analysis is based on records of 5,400 patients treated with crystalline penicillin G administered in aqueous solution or peanut oil and beeswax, with a total dosage of 2,400,000 to

116. Alexander, L. J.; Schoch, A. G., and Mantooth, W. B.: Abortive Treatment of Syphilis: Results Obtained in the Incubation, Primary, and Secondary Stages of Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **33**:429-436 (Sept.) 1949.

117. Bauer, T. J.; Usilton, L. J., and Price, E. V.: Rapid Treatment of Early Syphilis: Progress Report—June 1949, J. Ven. Dis. Inform. **31**:65-75 (March) 1950.

18,000,000 units. A total of 1,401 patients was observed for 21 months. Diagnosis at time of treatment was seronegative primary syphilis in 211 patients, seropositive primary syphilis in 348 and secondary syphilis in 842. Seronegativity rates at a 21 to 24 month observation period were 90.0, 85.9 and 78.7 per cent, respectively. The cumulative retreatment rates were 10, 12.2 and 15.6 per cent, respectively.

Preliminary results of evaluation of procaine penicillin in oil with 2 per cent aluminum monostearate are presented as a consequence of studies conducted by 16 cooperating clinics throughout the country. In seronegative primary syphilis, following a single injection of 300,000, 1,200,000 and 2,400,000 units of procaine penilicillin in aluminum monostearate, the cumulative retreatment rates at the fifteenth post-treatment month were 0, 32.3 and 0 per cent, respectively. When two injections of 1,200,000 units were administered at four or at seven day intervals, the rate of cure was 100 per cent. If four such injections were given at seven day intervals, the cumulative retreatment rate was 17.9 per cent, whereas 2,400,000 and 4,800,000 units of aqueous crystalline penicillin administered at two or three hour intervals had a retreatment rate of 6.7 and 7.4 per cent, respectively, for the 15 month post-treatment observation period. In seropositive primary syphilis single injections of 300,000, 1,200,000 and 2,400,000 units of procaine penicillin in 2 per cent aluminum monostearate had a cumulative retreatment rate of 18.5, 13.8 and 5 per cent at 15 months. When two injections of 1,200,000 units were given at four or seven day intervals, the retreatment rate was 9.1 and 1.3 per cent, respectively. If four injections of 1,200,000 units were given at seven day intervals, the retreatment rate was 15 per cent. Cumulative retreatment rates for 2,400,000 and 4,800,000 units of aqueous penicillin G were 9.4 and 13 per cent for an equivalent period. In secondary syphilis the cumulative retreatment rate at 15 months for patients receiving single injections of 300,000, 1,200,000 or 2,400,000 units of procaine penicillin in 2 per cent aluminum monostearate was higher, 19.6, 28.7 and 6.3 per cent, respectively. If two injections of 1,200,000 units of the preparation were given at four and seven day intervals, the retreatment rates were 5 and 12.5 per cent, respectively. When four injections of 1,200,000 units were administered at seven day intervals, the retreatment rate was 13.4 per cent. In contrast, 2,400,000 units of aqueous crystalline penicillin G given over an eight day period had cumulative retreatment rates of 12.8 and 10.2 per cent. From the limited data available it seems that doses totaling 2,400,000 units are more effective than the small dosage schedules in the treatment of secondary syphilis. Schedules providing both 1,200,000 and 2,400,000 units of procaine penicillin G in 2 per cent aluminum monostearate, whether administered as one or as two injections, compare favorably with the aqueous penicillin schedules of equivalent dosages. When the results are compared of two schedules employing 4,800,000 units of penicillin, whether administered as four injections of 1,200,000 units at weekly intervals or as aqueous penicillin every two to three hours for eight days, the cumulative retreatment rates are approximately the same throughout the observation period. The preliminary figures suggest that procaine penicillin administered in one, two and four injections may be effective in the treatment of early syphilis. A larger volume of cases and longer observation periods may be necessary to verify this initial impression.

Penicillin Plus Arsenical and/or Heavy Metal.—In the British Armed Forces the routine therapy of early syphilis for several years has been a course of treat-

ment with penicillin (usually a total of 4,000,000 to 4,800,000 units over a 10 day period) plus metal chemotherapy administered during and after the period of penicillin treatment. Eames and Miller [118] have recently reviewed the results of this form of therapy among army personnel, and Belcher [119] has summarized the experiences of the British Royal Navy. Among 1,028 army personnel treated for infectious early syphilis, the cumulative total "relapse" rate at six months was 5.7 per cent; at 12 months, 12.1 per cent, and at 18 months, 15.0 per cent. With the elimination of probable reinfections, these figures are respectively 5.2, 9.3 and 10.8 per cent. These results seem to be somewhat more satisfactory than those reported from therapy with comparable penicillin preparations alone or from penicillin plus arsenicals given only during the period of penicillin administration. It is interesting to note, however, that this slightly lower incidence of failures was achieved at the expense of incurring a 3.5 per cent incidence of toxic reactions attributable to the therapy. The data for the Royal Navy are quite similar. After treatment of 962 cases of infectious syphilis, and after an average observation period of 12 months, the over-all failure rate was 11.2 per cent and the incidence of toxic reactions (including one death) was 4.1 per cent.

Pardo-Castello and Pardo [120] also present a preliminary report on the treatment of early syphilis in their clinic in Habana, Cuba. Their figures seem to coincide with or approximate those reported by the Syphilis Study Group of the United States Public Health Service, yet their technic is quite different. They employ far larger total dosage (10,000,000 units of penicillin G), a more prolonged treatment period (20 days), an aqueous menstruum rather than oil and biweekly injections of 0.13 Gm. of bismuth subsalicylate for 10 to 20 weeks. The report is unusual at this time, when, as pointed out by Rein,[121] accumulated data seem to indicate that (1) there is no added advantage in the employment of adjuvant heavy metal therapy; (2) better results have been obtained in shorter periods with procaine penicillin G in aluminum monostearate and oil than with aqueous solutions of sodium salts of penicillin, and (3) the number of patients who lapse from therapy increases as the duration of therapy is prolonged.

Penicillin and Fever Therapy.—Plotke, Schwemlein, Craig and Rodriquez [122] treated 148 patients who had dark field–positive primary or secondary syphilis with 2,400,000 units of sodium penicillin over 7½ days and three hours of artificial fever (rectal temperature of 106 F.) every other day, beginning 23 hours after penicillin administration was started. Of the patients with seropositive syphilis, 80.8 per cent

118. Eames, J. W., and Miller, D. H.: Treatment of Early Syphilis with Penicillin Combined with Neoarsphenamine and Bismuth, Brit. M. J. **2**:672-676 (Sept. 24) 1949.

119. Belcher, H. L.: Report of the Central Syphilis Register, July 1949, J. Roy. Nav. M. Serv. **35**:280-292 (Oct.) 1949.

120. (*a*) Pardo-Castello, V., and Pardo, O. A.: Treatment of Early Syphilis with Penicillin and Bismuth Subsalicylate: Daily Injection of 500,000 Units of Penicillin G in Sodium Chloride Solution for 20 Consecutive Days and 10 to 20 Doses of Bismuth Subsalicylate at the Rate of 2 a Week, Arch. Dermat. & Syph. **61**:196-209 (Feb.) 1950. (*b*) Castanedo y Pardo, C., and Pardo-Castello, V.: Tratamiento de la sifilis, Médica, Matanzas **8**:110-118 (Sept.-Oct.) 1949.

121. Rein, C. R., in discussion on Pardo-Castello and Pardo.[11a]

122. Plotke, F.; Schwemlein, G. X.; Craig, R. M., Rodriquez, J.: Penicillin and Fever Therapy in Early Syphilis: A Report of 161 Patients Treated with 2.4 Million Units of Penicillin and Physically Induced Fever, Am. J. Syph., Gonor. & Ven. Dis. **34**:161-166 (March) 1950.

reversed to seronegativity. The median time required to reach seronegativity was 120 days. A lumbar puncture was performed on 142 patients prior to treatment. There were 14 (9.9 per cent) abnormal spinal fluids. Of 25 patients with normal pretreatment fluids in whom treatment failed, 22 were reexamined at the time of failure and five showed evidence of activity. The cumulative failure rate at the end of the 12 to 15 month observation period for 95 patients who received 2,400,000 units of penicillin in 7½ days, combined with three sessions of artificial fever, was 20.2 per cent, as compared with 26.8 per cent for 266 patients treated with the same amount of penicillin alone. Corresponding failure rates at the 24 to 27 month period were 28.7 and 37.5 per cent, respectively. The difference in the results of the two schedules conforms to the general trend consistently noted in previous studies, that the addition of fever increases the effectiveness of penicillin therapy schedules and lends further credence to the in vitro studies showing the synergism of penicillin and fever.

Administration of Aqueous Sodium Penicillin (1,200,000 Units) Alone.—At the Chicago Intensive Treatment Center, under a contract recommended by the Committee on Medical Research, Barton and his co-workers[123] treated 324 patients having dark field–positive syphilis with 20,000 units of sodium penicillin in aqueous solution injected intramuscularly every three hours for a total of 60 injections, or 1,200,000 units of penicillin. The period of treatment was 7½ days. Observation of these patients extended from a minimum of 16 months to a maximum of 23 months. The cumulative failure rate, disregarding stages of the disease, was 29.6 per cent.

Administration of 2,400,000 Units of Penicillin Alone.—Bundesen and co-workers[124] report the results obtained when 639 patients with dark field–positive primary and secondary syphilis were treated with 2,400,000 units of aqueous sodium penicillin. The antibiotic was administered intramuscularly in doses of 40,000 units every three hours over a period of 7½ days. The cumulative failure rate at the end of two years was 23.2 per cent among 92 patients with primary seronegative syphilis, 26.9 per cent among 179 patients with primary seropositive syphilis, 37.5 per cent among 266 patients with untreated secondary syphilis and 33.6 per cent among 102 patients who had had some previous treatment and subsequently relapsed. The over-all failure rate was 32.2 per cent at the end of a 27 month observation period. In comparison with other similar groups treated at the same center, the over-all failure rate in 330 patients treated with a total of 600,000 units of sodium penicillin in 7½ days was 39.8 per cent at the end of two years. In a group of 323 patients receiving a total of 1,200,000 units by the same method, the failure rate was 31.1 per cent at the end of two years. The authors conclude that a schedule consisting of 2,400,000 units of penicillin is inadequate therapy for early infectious syphilis. It must be remembered

123. Barton, R. L.; Bauer, T. J.; Craig, R. M., and Schwemlein, G. X.: Treatment of Early Syphilis with Penicillin; Report on 324 Patients Treated with 1,200,000 Units over 7½ Days, Arch. Dermat. & Syph. **60**:150-154 (Aug.) 1949.

124. Bundesen, H. N.; Plotke, F.; Schwemlein, G. X., and Rodriquez, J.: Penicillin in the Treatment of Early Syphilis: 639 Patients Treated with 2,400,000 Units of Sodium Penicillin in 7½ Days, J. Ven. Dis. Inform. **30**:321-325 (Nov.) 1949.

that penicillin from 1943 on has been changing. The content of impurities has gradually decreased, and the potency in terms of units per milligram has increased. Such changes may have affected the results reported.

Therapeutic Results of Crystalline Penicillin G Versus Amorphous Penicillin.—Schwemlein, Plotke and Rodriquez [125] compare the cumulative percentage rates for success and failure in patients with early syphilis treated with 2,400,000 units of crystalline penicillin G and amorphous penicillin on the same time-dosage schedule. In earlier schedules, when 266 patients with secondary syphilis were given 2,400,000 units of amorphous penicillin in 7½ days, the cumulative failure rate was 26.8 per cent at the end of the 12 to 15 month observation period. When the same dosage was given over a 15 day period in 63 patients with secondary syphilis, the failure rate was 24.2 per cent for the same observation period. When 2,400,000 units of crystalline penicillin G was administered to a group of 35 patients with primary seronegative syphilis, the cumulative failure rate (reinfection and relapse) was 12 per cent at a 12 to 15 month observation period. Fifty-six patients with seropositive primary syphilis had a total failure rate of 19.4 per cent. In secondary syphilis the 79 patients showed a cumulative failure rate of 15.6 per cent. A total of 179 patients had a cumulative failure rate of 16.2 per cent after 12 to 15 months. This study illustrates that in the treatment of early syphilis crystalline penicillin G is therapeutically more effective than the amorphous penicillin.

Penicillin in Oil and Wax.—Rauschkolb and Cole [126] treated 160 patients with primary and secondary syphilis and 15 patients with early latent syphilis with daily injections of 600,000 units of penicillin in white wax and oil for a total dosage of 4,800,000 units. This dosage permitted a relapse rate of 31.03 per cent (based on 116 patients who were followed adequately). Of those who had a relapse, 20, or 55.5 per cent, were recognized as having a clinical relapse, 11, or 30.5 per cent, as being seropersistent and 5, or 13.5 per cent, as having a serorelapse.

Shaffer and Courville [127] discuss the results of a project begun in March 1946 by the Venereal Disease Committee of the National Research Council. A schedule of treatment was assigned to Wayne University College of Medicine and the Social Hygiene Clinic of the Detroit Department of Health. It consisted of the intramuscular administration, twice weekly, of 600,000 units of penicillin G in peanut oil and wax (Romansky formula). Seventy patients with early syphilis were treated according to this schedule, and, following 24 to 32 months of observation, the cumulative failure rate has been 11.3 per cent. The schedule used in this study offers an interesting introduction to similar schedules now in use but employing the newer penicillin preparations of the repository type.

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125. Schwemlein, G. X.; Plotke, F., and Rodriquez, J.: Crystalline Penicillin G Versus Amorphous Penicillin: Treatment of Early Syphilis, J. Ven. Dis. Inform. **31**:155-159 (June) 1950.

126. Rauschkolb, J. E., and Cole, H. N.: Treatment of Syphilis with Penicillin Injection in Oil and Wax U.S.P.: Analysis of 153 Cases, Arch. Dermat. & Syph. **60**:676-689 (Nov., pt. 1) 1949.

127. Shaffer, L. W., and Courville, C. J.: Treatment of Early Syphilis with Penicillin G: Administration of Penicillin G in Peanut Oil and Wax Twice Weekly for 8 Weeks, Arch. Dermat. & Syph. **60**:253-260 (Aug.) 1949.

Procaine Penicillin in Oil with 2 per Cent Aluminum Monostearate.—Thomas, Rein and Kitchen [128] used four treatment schedules for early syphilis: Schedule 1 provided a single injection of 4 cc. (1,200,000 units); schedule 2 provided a single injection of 8 cc. (2,400,000 units); schedule 3 provided a single injection of 4 cc. once a week for two weeks (2,400,000 units); schedule 4 provided a single injection of 4 cc. once a week for four weeks (4,800,000 units). One hundred and sixty patients with primary and secondary syphilis were selected for this study and divided into the four treatment groups mentioned above. Nineteen patients were lost from observation, and an additional 17 patients were followed for less than three months. Of the remaining 124 cases, three were classified as failures, one of which was a reinfection. Although the number of patients treated in each schedule is too few and the period of follow-up too short to allow for any definite conclusions, there appears to be a satisfactory trend. No instance of undue irritation or untoward effect was reported by or observed in patients on any of these four schedules. Several patients who received 8 cc. in one depot reported moderate pain during and for a short time following the injection. The incidence of generalized allergic reactions encountered in the authors' experience to date is about 0.2 per cent.

"Infectious Failure" After Penicillin Therapy of Early Syphilis.—After treating 1,105 patients who had early syphilis with penicillin given according to five different treatment schedules, Schoch and Alexander [129] found that 137 of their patients later exhibited evidence of "infectious failure." The term "infectious failure" was used to describe all cases in which, months or years after treatment with penicillin for early syphilis, patients exhibited dark field–positive lesions morphologically typical of primary and/or secondary syphilis. After the 137 cases were subjected to critical and detailed collective and individual analysis, the diagnosis of reinfection was made in 80, leaving 57 in the category of relapse. On the basis of data collected for this study Schoch and Alexander concluded:

> Reinfection is more prevalent than infectious relapse.
>
> For practical purposes of differentiation, any patient who presents clinical signs of infectious syphilis one year or more after penicillin treatment for early syphilis should be regarded as having a reinfection rather than an infectious relapse.
>
> The treatment of reinfection is more successful than the treatment of early syphilis in general.
>
> Since we have made a diagnosis of reinfection in the majority of instances, we disapprove of grouping together patients with reinfection and patients with infectious relapse as representing "infectious failure."
>
> The diagnosis of reinfection is relatively simple, provided adequate subjective and objective data are available. We have particular reference to serologic titer curves and positive epidemiologic findings.

Relationship of Clinical Failure to Serologic Response in Penicillin-Treated Early Syphilis.—Hoekenga, Buerk and Rider [130] analyzed records of the 38 par-

128. Thomas, E. W.; Rein, C. R., and Kitchen, D. K.: Experiences with Single and Multiple Treatment Schedules of Early Syphilis with Procaine Penicillin in Oil and Aluminum Monostearate, Am. J. Syph., Gonor. & Ven. Dis. **33**:523-526 (Nov.) 1949.

129. Schoch, A. G., and Alexander, L. J.: Reinfection and Relapse After Treatment of Early Syphilis with Penicillin: Analysis of 137 Cases of "Infectious Failure" in a Total Series of 1,105 Cases, Arch. Dermat. & Syph. **60**:690-700 (Nov., pt. 1) 1949.

130. Hoekenga, M. T.; Buerk, M. S., and Rider, R. V.: The Relationship of Early Clinical Failure to Serologic Response in Penicillin-Treated Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **33**:323-333 (July) 1949.

ticipating clinics in the nationwide penicillin study from 1943 to 1947, which was under the direction of the Penicillin Panel of the Subcommittee of Venereal Disease, National Research Council, and later under that of the Syphilis Study Section of the National Institutes of Health. The records were made available at the Central Statistical Unit of the Department of Statistics, Johns Hopkins School of Hygiene and Public Health. From the 23,322 records examined, 16,150 were selected for analysis of the serologic pattern; the remaining 7,172 cases were omitted because of inadequate serologic follow-up. Of the 16,150 cases approximately 600 were retreated prior to clinical failure, leaving a total of 15,550 cases observed for serologic and clinical failure. In order to make a comparison of the serologic results with immediate clinical results, the records were divided into five groups. Group I was composed of 1,741 cases of seronegative primary syphilis that remained seronegative for the first post-treatment year. The cumulative clinical failure rate at 12 months was 3 per cent, at 18 months 5.5 per cent and at 36 months 9.7 per cent. Group II was composed of 7,348 cases of seropositive early primary and secondary syphilis that attained seronegativity within the first year. The cumulative clinical failure rate at 12 months was 0.8 per cent, at 18 months 3.1 per cent and at 36 months 7.7 per cent. Group III was composed of 4,195 cases of seropositive early syphilis still seropositive but attaining a low titer during the first post-treatment year. The cumulative clinical failure rate at 12 months was 3.8 per cent, at 18 months 6.4 per cent and at 36 months 12.9 per cent. Group IV consisted of 489 cases of seropositive early syphilis still showing seropositivity of high titer at the end of the first post-treatment year. The cumulative failure rate was 26.7 per cent at 12 months and 29.9 per cent at 18 months. Group V was composed of 1,777 cases of early syphilis whether seronegative or seropositive in which serologic relapse developed before the end of the first post-treatment year (without previous evidence of clinical failure). The cumulative clinical failure rate was 71.5 per cent at 12 months and 75.1 per cent at 18 months. In those cases still seropositive (low titer of 8 dilution units or less) at the end of the first year that had shown no indication of serologic or clinical relapse, spontaneous seronegativity was attained in 40 per cent during the second post-treatment year, 61 per cent became seronegative during the third year and nearly 70 per cent became seronegative by the end of the fourth post-treatment year. In decided contrast, if the serologic reaction remained in high titer (50 per cent or more of the original titer), the failure rate was five to six times as high or about 30 per cent at 18 months. If serologic relapse occurred and retreatment was withheld, the clinical failure rate mounted to 75 per cent by the eighteenth post-treatment month.

The authors emphasize the importance of clinical inspection of the penicillin-treated patient, as well as a quantitative serologic test, in the post-treatment observation period. Reliance on serologic progress alone is insufficient. With this in mind, certain statements of practical importance may be made about the necessity of retreatment of the penicillin-treated patient with early syphilis who shows no signs of clinical relapse. These are as follows: 1. In seronegative primary or seropositive early syphilis retreatment is unnecessary if the patient remains or becomes and remains seronegative. 2. In seropositive early syphilis retreatment is not necessary because of a weakly positive reaction (25 per cent of original titer or

8 dilution units or less) during the first year after therapy. 3. If the serologic reaction persists for six months on higher titer (greater than 25 per cent or more of the original titer) retreatment should be given at six months, regardless of whether clinical relapse has or has not appeared. 4. Patients with serologic relapse should in all cases be retreated as soon as the fact of such relapse is confirmed by repeated serologic tests (two or more, to rule out laboratory error).

Thomas and Landy [131] report the data on 689 patients who relapsed or were reinfected one or more times following penicillin therapy of dark field–positive early syphilis at the Rapid Treatment Center at Bellevue Hospital, New York, between December 1943 and October 1947. In addition to the 689 patients who relapsed or were reinfected, 36 patients were retreated one or more times for so-called seroresistance, and one was retreated for asymptomatic neurosyphilis. Of the 689 retreated patients, 409 have been followed for 12 to 56 months after retreatment. Of 409 patients followed for one or more years after the last retreatment, 81.4 per cent had negative serologic reactions when last examined, 16.4 per cent had blood Kahn titers of 8 or less and 2.2 per cent had Kahn titers of 16. Of the 409 patients followed, all but 17 have had at least one spinal fluid examination; only 291 had spinal fluid examinations one or more years after the last retreatment. All these 291 spinal fluid examinations gave normal results. One patient with pleocytosis at the time of the fourth retreatment has had no subsequent spinal fluid examination. Of the 689 patients retreated at least once, 27.4 per cent had a chancre at the first retreatment and an additional 10 per cent admitted exposure to persons with known infectious early syphilis. Of 107 patients retreated at least twice, 24.3 per cent had a chancre at the time of the second retreatment and an additional 7.5 per cent admitted exposure to persons with known infectious early syphilis. Of 20 patients retreated at least three times, 25 per cent had a chancre at the third retreatment and an additional 20 per cent admitted exposure to persons with known early infectious syphilis. Of the 689 patients retreated at least once, 44.1 per cent had negative serologic reactions for varying periods up to 53 months prior to the first retreatment. Of 107 patients retreated a second time, 30 per cent showed negative reactions for varying periods up to 46 months prior to the second treatment. Of the 20 patients retreated at least three times, 35 per cent had negative reactions for varying periods up to 18 months prior to the third retreatment. In the opinion of the authors over 50 per cent of the retreatments were due to reinfection rather than to relapse, although the only absolute proof of reinfection is the development of a new chancre at a new site following treatment of early syphilis. One patient with a persistent blood Kahn titer of 3 was found to have asymptomatic neurosyphilis 30 months after treatment for secondary syphilis. Eleven months after retreatment the cells and total protein in the spinal fluid were normal, but the spinal fluid Wassermann reaction was positive.

Spinal Fluid Findings in Relapsing Early Syphilis.—Sackett and Boggs [132] report on 437 patients with early syphilis who relapsed following penicillin therapy.

131. Thomas, E. W., and Landy, S.: Report on 726 Patients Who Were Re-Treated Following Penicillin Therapy for Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **34**:126-143 (March) 1950.

132. Sackett, A. P., and Boggs, H.: A Report of Spinal Fluid Findings in Patients Who "Relapsed" Following Penicillin Therapy in Early Syphilis, J. Ven. Dis. Inform. **30**:219-223 (Aug.) 1949.

The group included 349 patients with primary or secondary syphilis and 88 patients with early latent syphilis. Only patients with spinal fluid examinations on first admission and on readmission were included in the study. Seven treatment schedules were used for these patients. The results of this study are based on the older treatment schedules which are no longer employed and, therefore, are not comparable with present day therapeutic results. Secondly, no attempt was made to determine whether these cases were relapses or reinfections.

Penicillin-Resistant Early Syphilis.—Wexler and others [133] report the case of a 24 year old Negro soldier who received 100,000 units of crystalline sodium penicillin every three hours for 80 injections (total dose was 8,000,000 units) after dark field–positive, seropositive primary syphilis was diagnosed. On the last day of treatment an edematous reaction of the prepuce and a papular, erythematous symmetrical eruption developed. Dark field examination of the papules revealed living T. pallidum. His condition responded favorably, both clinically and serologically, to treatment with oxophenarsine hydrochloride and bismuth subsalicylate.

TREATMENT OF LATE SYPHILIS

Syphilitic Paroxysmal Cold Hemoglobinuria.—Glushien [134] reports syphilitic paroxysmal cold hemoglobinuria of 41 years' duration in a 50 year old Negro man with syphilitic heart disease. Although the author states that this patient had no stigmas of congenital syphilis, an otologist found evidence of bilateral eighth nerve disease which he ascribed to syphilis. A spinal fluid examination was refused. The author believes that the presence of syphilitic paroxysmal cold hemoglobinuria does not indicate immunity to spirochetal invasion and is a reason for prescribing, rather than for withholding, antisyphilitic therapy. He also states that paroxysmal cold hemoglobinuria may occur for many years without significantly impairing renal function.

Wiggall [135] reports the results of treatment with penicillin of four patients with paroxysmal cold hemoglobinuria. The first patient remained well 38 months post treatment, and exposure to cold failed to precipitate hemoglobinuria. The second patient, observed for 23 months, did not benefit from treatment. The third patient, followed for 14 months, was benefited in that he had mild hemoglobinuria only on prolonged exposure to cold. The fourth patient received no benefit as observed for one month. Cold hemolysins persisted in all patients.

Nichols and Williams [136] report a case of early dementia paralytica associated with paroxysmal cold hemoglobinuria. The patient was treated with 4,800,000 units of penicillin with "complete clinical recovery" following therapy. Although no definite statement concerning the follow-up period is made in the report, it was observed that cold hemolysins persisted in the serum following therapy.

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133. Wexler, L.; Bugg, R. N.; Adams, H. V., and Smith, A. D.: Penicillin-Resistant Early Syphilis: Report of a Case, Arch. Dermat. & Syph. **60**:1207-1208 (Dec.) 1949.

134. Glushien, A. S.: Syphilitic Paroxysmal Cold Hemoglobinuria of 41 Years' Duration Associated with Syphilitic Heart Disease, Am. J. Syph., Gonor. & Ven. Dis. **33**:444-449 (Sept.) 1949.

135. Wiggall, R. H.: Penicillin Treatment of Paroxysmal Cold Hemoglobinuria, Am. J. Syph., Gonor. & Ven. Dis. **33**:450-453 (Sept.) 1949.

136. Nichols, F. T., and Williams, C. J.: Paroxysmal Cold Hemoglobinuria Associated with Dementia Paralytica: Report of Treatment with Penicillin, J. A. M. A. **140**:1322-1324 (Aug. 27) 1949.

Banti's Syndrome.—Hambrick and Smith [137] reported two cases of Banti's syndrome occurring in patients with syphilis.

THERAPY OF CARDIOVASCULAR SYPHILIS

Penicillin therapy is now the accepted procedure for cardiovascular syphilis. In spite of such careful studies as that of Gerbaux,[138] extolling the mercury cyanide treatment of aortitis, enthusiastic but well investigated series of cases of penicillin-treated cardiovascular syphilis have indicated the safety and practicality of this form of treatment without a doubt. Several of these reports are herewith detailed.

Coale and his co-workers [139] treated 70 patients who had various types of cardiovascular syphilis with penicillin; 47 of the patients were previously treated with metal preparations; the other 23 had had no previous treatment. The authors feel that penicillin therapy of cardiovascular syphilis is a safe procedure without the necessity of previous preparation with heavy metals or iodides. The theoretical dangers of therapeutic shock and therapeutic paradox are not clinically important enough to warrant delaying use of the antibiotic in any case. Therapy consisted of 6,000,000 units in most patients, administered in an absorption-delaying base in 65 of them. Favorable serologic response was obtained in about 50 per cent of the patients.

In a series of 78 male patients from 35 to 58 years of age with cardiovascular syphilis to whom full doses of penicillin were administered from the start of therapy, Russek and his co-workers [140] observed no instances of therapeutic shock. All the patients were hospitalized except for a small number treated in private practice. Penicillin was administered in aqueous solution to 58 patients in a dosage of 40,000 units every two hours for 85 doses, while the remaining 20 patients received 600,000 units of penicillin in oil with aluminum monostearate daily for six days. Methods employing graded doses of spirocheticidal drugs or preparatory courses of treatment with iodides and heavy metals are probably without prophylactic value with respect to such reactions. Penicillin may be safely administered in cardiovascular syphilis in unrestricted dosage. Hayward,[141] while agreeing with the value of penicillin, still suggests two or three months' preparation with bismuth and iodides prior to the administration of 8,000,000 to 10,000,000 units of penicillin.

Flaum and Thomas [142] treated 39 patients who had cardiovascular syphilis with penicillin in full dosage from the start of treatment without untoward reactions attributable to the antibiotic. Patients who had not received previous antisyphilitic

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137. Hambrick, G. W., Jr., and Smith, C. D.: Advanced Banti's Syndrome Associated with Syphilis: Review and Report of Failure of Penicillin Therapy in 2 Cases, Am. J. Syph., Gonor. & Ven. Dis. **33**:476-480 (Sept.) 1949.

138. Gerbaux, A.: Le traitement de l'aortite syphilitique par le cyanure de mercure en cures très prolongées, Semaine d. hôp. Paris **25**:3125-3136 (Oct. 14) 1949.

139. Coale, L. H.; Allen, M. S., and Delp, M. H.: Penicillin Treatment of Cardiovascular Syphilis, J. Kansas M. Soc. **51**:102-109 (March) 1950.

140. Russek, H. I.; Nicholson, F. P., and Zohman, B. L.: Penicillin in Cardiovascular Syphilis, New York State J. Med. **49**:2176-2177 (Sept. 15) 1949.

141. Hayward, G. W.: Advances in the Treatment of Heart Disease, Post-Grad. M. J. **25**:537-542 (Nov.) 1949.

142. Flaum, G., and Thomas, E. W.: Penicillin Therapy of Cardiovascular Syphilis, Am. Heart J. **38**:361-366 (Sept.) 1949.

therapy were given three injections of 0.2 Gm. of bismuth subsalicylate in oil, five days apart, before institution of penicillin treatment. Thirty of the patients had syphilitic aortic insufficiency; four had saccular aneurysm, and five had diffuse aneurysmal dilatation of the aorta. Although penicillin therapy produced no notable untoward reactions, the authors believe that it is advisable to administer a bismuth preparation prior to the penicillin to patients who have had no previous antisyphilitic treatment.

Forsey [143] states that there is still doubt in the minds of many clinicians and syphilologists concerning the efficacy of specific therapy in aortic regurgitation and aneurysm. He has reviewed five series of cases of cardiovascular syphilis treated with penicillin and summarized the data. Critical analysis of the 161 cases reported reveals that many were diagnosed as aortitis, a notoriously difficult clinical diagnosis to make, and most of the patients had received previous treatment. When only "virgin" cases were considered, 25 cases of aortic insufficiency and 11 cases of aortic aneurysm were left. In these reports there were no instances of serious reaction, and in no case was it necessary to discontinue therapy. Furthermore, the presence of decompensation did not seem to be any contraindication for penicillin. Forsey concludes that penicillin is a powerful drug which is definitely known to produce therapeutic shock in a large percentage of cases. It will also produce rapid healing with a resultant scar. The dangers of intensive treatment have been laid down on sound physiological and pathological grounds; yet the evidence to date seems to indicate that these dangers have been overemphasized. However, until the value of penicillin therapy alone is shown to be superior in terms of reduction of symptoms and increased survival to a regimen in which time is taken for adequate preparation, the risk, no matter how slight, is not justified except as a purely experimental problem.

Penicillin Therapy of Cardiovascular Syphilis in Congestive Failure.—Edeiken, Ford, Falk and Stokes,[144] of the University of Pennsylvania, treated 12 patients with syphilitic cardiovascular disease and congestive failure. In two of them initial doses of 500 units of aqueous penicillin were given every two hours. The remaining 10 received large initial doses. The total dose ranged from 4,800,000 to 9,600,000 units of aqueous penicillin G. None of the 12 patients was prepared with less potent spirocheticidal drugs. All were closely observed in the hospital while at complete rest in bed and on a low salt diet. Administration of digitalis, ammonium chloride and mercurial diuretics was started at the same time as that of penicillin for all but one patient. Electrocardiograms were made at intervals of three days. No untoward reactions were observed. Two patients had a slight febrile reaction six and 16 hours, respectively, after the start of treatment. None of the patients showed increased evidence of congestive failure, but all showed symptomatic improvement within 48 to 72 hours after onset of treatment. Electrocardiographic studies revealed T wave abnormalities and other changes which could be attributed to digitalis, but in no instance was there evidence of intraventricular conduction defects. All the patients were able to leave the hospital immediately after completion of penicillin therapy (usually 12 days) in an

143. Forsey, R. R.: The Problem of Specific Therapy in Cardiovascular Syphilis, Canad. M. A. J. **62**:339-341 (April) 1950.

144. Edeiken, J.; Ford, W. T.; Falk, M. S., and Stokes, J. H.: Penicillin Treatment of Patients with Cardiovascular Syphilis in Congestive Failure, Circulation **1**:1355-1361 (June) 1950.

improved state. Two of them died two months following the completion of penicillin therapy. It was the impression of the authors that patients with syphilitic cardiovascular disease in cardiac failure who are given the combined therapy with penicillin react better than those who receive only treatment for congestive failure.

Polythene Cellophane® Treatment of Aneurysm.—In a preliminary report from the Department of Surgery (Thoracic), of Emory University School of Medicine, Emory University, Ga., the predominant lesion treated by the application of polythene cellophane® to aneurysms of the intrathoracic vessels was aneurysmal disease secondary to syphilitic aortitis. Twenty-three patients, most of them with lesions of syphilitic origin, were treated by this method, more beneficial results being obtained in those patients with lesions that could be surrounded by polythene cellophane.® Abbott [145] has applied cellophane® in 32 instances of thoracic aneurysms, mostly syphilitic, using internal wiring technic in four, the most benefit being obtained in those cases in which the lesion could be surrounded by the cellophane.®

TREATMENT OF NEUROSYPHILIS

Penicillin reigns supreme in the therapy of neurosyphilis. The adjunctive use of fever therapy is apparently an unnecessary hazard. Intrathecal administration not only is dangerous but serves no useful purpose in treatment of neurosyphilis, since penicillin given intramuscularly penetrates into the cerebrospinal fluid in adequate bactericidal amounts.[146] A number of general studies on the treatment of neurosyphilis with penicillin has appeared,[147] as well as studies on various specific types of neurosyphilis [148] and treatment failures.[149]

145. Abbott, O. A.: Clinical Experiences with the Application of Polythene Cellophane upon Aneurysms of the Thoracic Vessels (Syphilis), J. Thoracic Surg. **18**:435-461 (Aug.) 1949.

146. Redfearn, J. W. T.; Elithorn, A.; Till, K., and Ibbott, F. A.: Penicillin in the Cerebrospinal Fluid, Lancet **2**:652-656 (Oct. 8) 1949.

147. (*a*) Susman, E.: Treatment of Neurosyphilis, M. J. Australia **2**:829-833 (Dec. 10) 1949. (*b*) Sexton, G. B.: Modern Treatment of Neurosyphilis, Canad. M. A. J. **62**:43 (Jan.) 1950. (*c*) Packer, H., and Wong, Y. T.: Penicillin and Penicillin-Malaria in the Treatment of Tabes Dorsalis, Ann. Int. Med. **31**:96-104 (July) 1949. (*d*) Breutsch, W. L.: Penicillin or Malaria Therapy in the Treatment of General Paralysis? (A Clinico-Anatomic Study), Dis. Nerv. System **10**:368-371 (Dec.) 1949. (*e*) Spiller, W. F., and Stewart, J.: Neurosyphilis: Comparative Treatment with Penicillin Alone and Penicillin Plus Malaria, J. Invest. Dermat. **14**:121 (Feb.) 1950. (*f*) Curtis, A. C.; Kruse, W. T., and Norton, D. H.: Neurosyphilis: III. Evaluation After 3 Years of Treatment with Penicillin Alone and with a Combination of Penicillin and Malaria, Am. J. Syph., Gonor. & Ven. Dis. **33**:527-536 (Nov.) 1949. (*g*) Epstein, N. N., and Key, J. M.: Treatment of Neurosyphilis with Penicillin Combined with Artificial Fever, Arch. Dermat. & Syph. **60**:543-557 (Oct.) 1949. (*h*) Stokes, J. H.; Falk, M. S., and Gammon, G. D.: Effect of 5 Years of Penicillin Alone on Neurosyphilis, Including Some Comparisons with Prepenicillin Methods, Am. J. Syph., Gonor. & Ven. Dis. **33**:537-560 (Nov.) 1949. (*i*) Goldman, D.: Neurosyphilis Treated with Penicillin: Report of 140 Cases, J. A. M. A. **141**:431-438 (Oct. 15) 1949.

148. (*a*) Nichols, F. T., Jr., and Heyman, A.: Penicillin Therapy in Asymptomatic Neurosyphilis: A Comparison of the Effects of Amorphous Penicillin, Penicillin in Oil and Wax, and Crystalline Penicillin G, Am. J. Syph., Gonor. & Ven. Dis. **33**:561-570 (Nov.) 1949. (*b*) Koteen, H.: Difficulties in the Evaluation of Treatment Procedures in Tabes Dorsalis, ibid. **33**:364-379 (July) 1949.

149. (*a*) Landau, D.; Kopp, I.; Rose, A. S., and Solomon, H. C.: Penicillin Treatment of Late Neurosyphilis: One- to Five-Year Follow-Up with Special Reference to Clinical Failures, Am. J. Syph., Gonor. & Ven. Dis. **33**:357-363 (July) 1949. (*b*) Dattner, B.: Penicillin Failures in Neurosyphilis, ibid. **33**:571-575 (Nov.) 1949.

Gammon and his associates [150] report the autopsy observations in seven cases of penicillin-treated neurosyphilis. There were 3 patients with dementia paralytica; the brain of one, who died three weeks after receiving 2,400,000 units of penicillin, showed at necropsy the appearance of the active disease. Examination of the other two paretics (both died about five months after receiving penicillin) showed loss of nerve cells but only a slight lymphocytic infiltrate. One patient with meningovascular syphilis died of acute myelogenous leukemia five months after receiving his penicillin. The brain showed arteriosclerotic changes but no round cell infiltration. The spinal cord exhibited a few patchy areas of degeneration not typical of tabes. The remaining three patients were tabetic. They all displayed typical posterior column degeneration, but no evidence of active inflammation was seen. The pathological observations bear out the clinical and humoral results obtained in the treatment of neurosyphilis, that is, the clearing of the infectious process. Two other cases are presented, one of acute multiple sclerosis and the other of a hypertensive cerebrovascular accident. In both cases there were strong positive spinal fluid Kolmer reactions, felt to represent false positive results.

Dattner-Thomas Formula.—During the past four years Horne [151] treated 11 patients who had spinal fluid abnormalities of the Dattner-Thomas type. These patients were followed for 10 to 39 months subsequent to treatment. Five of the 11 patients were treated with penicillin alone and six with penicillin and malaria. Treatment resulted in clinical (objective and/or subjective) improvement in 10 patients, and four patients had completely normal results on spinal fluid examinations. The author concluded that the validity of withholding treatment in such cases is open to question, because of the improvement observed in the patients receiving treatment. We concur in this view.

Treatment of Tabes Dorsalis with Penicillin and Penicillin Plus Malaria.—Packer and Wong [147c] gave 15 of 30 patients with tabes dorsalis penicillin alone (sodium salt in doses of 30,000 units every three hours day and night, average dose 6,200,000 units), and the remainder received penicillin throughout the febrile course of malarial therapy (rectal temperature above 103 F. for average of 47 hours and an average of 5,250,000 units of penicillin per patient). The average duration of the symptoms was longer in the group given malaria and penicillin therapy. The results of this study suggested that for rapidly progressive optic atrophy and for severe gastric crises combined penicillin-malaria treatment probably is best, but for other clinical manifestations of tabes dorsalis penicillin alone appears to offer results approaching those achieved by combined therapy.

In a study at the Central State Hospital, Indianapolis, Breutsch [147d] included the comparison of a group of patients having dementia paralytica treated with 10,000,000 units of penicillin (50,000 units given intramuscularly every three hours) with a group of similar patients treated with malaria alone. Since with administration of 10,000,000 units spirochetes were present in the brain at autopsy,

150. Gammon, G. D.; Lewey, F. H.; Dillon, H.; Schwarz, G., and Stokes, J. H.: Pathologic Observations of Penicillin-Treated Neurosyphilis, Am. J. Syph., Gonor. & Ven. Dis. **34**:227-235 (May) 1950.

151. Horne, S. F.: The Validity of Withholding Treatment in the Presence of Dattner-Thomas Formula in the Spinal Fluid, Am. J. Syph., Gonor. & Ven. Dis. **33**:454-461 (Sept.) 1949.

use of 15,000,000 units is recommended for reasons of safety. The impression was that the effect of penicillin at least equals, if not excels, that of malaria therapy when administered in sufficient amounts.

Spiller and Stewart [147e] report that 251 patients with various types of neurosyphilis were treated at the Cleveland City Hospital and University Hospital since 1944 with penicillin alone or in combination with malaria. One hundred and seventy patients were followed for periods of six months to four years or more. One hundred and five patients were treated with penicillin alone. A total of 2,000,000 to 9,600,000 units was given in doses of 40,000 to 80,000 units intramuscularly every three hours for 8, 15 or 20 days. Sixty-five patients were treated with penicillin plus malaria (20 hours of rectal temperature over 40 C. [104 F.]). The authors report that in the various types of neurosyphilis the spinal fluid findings responded equally well to both schedules of treatment.

Comparison of Penicillin and Malaria in the Treatment of Neurosyphilis.—Curtis, Kruse and Norton,[147f] who report on the post-treatment observation of 380 patients with various types of neurosyphilis that received either penicillin alone or a combination of penicillin and malaria, also felt that patients with various types of central nervous system syphilis, including dementia paralytica, respond as well to penicillin alone as to penicillin and malaria.

Effect of Penicillin Alone on Neurosyphilis.—Stokes, Falk and Gammon [147h] of the University of Pennsylvania Penicillin Panel, present a report on five years' experience with penicillin alone in the treatment of a group of patients with neurosyphilis. The improvement figures on the spinal fluid (normal or near normal) previously attained were held or slightly improved in 1948 and ranged from 53 per cent in dementia paralytica to 80 per cent in tabes dorsalis and in asymptomatic neurosyphilis. Meningovascular neurosyphilis showed slightly poorer long term spinal fluid results than any other type. Retreatment of relapse or slow response with larger total doses (approximating 10,000,000 units in two hour, around the clock hospitalization sessions at 80,000 to 100,000 units per injection of crystalline penicillin G) was found necessary. A total dosage of 18,000,000 units in several courses was used. Lasting results may follow much smaller dosage. In any phase of neurosyphilis, including dementia paralytica, there is hope for arrest by penicillin treatment up to five years' observation. Serologic cures without clinical improvement, and the reverse, may be obtained. The Dattner-Thomas type of fluid of long standing may respond (perhaps only temporarily) to repeated penicillin therapy. Improvement and five year arrest of progressive and relapsing primary optic atrophy in the tabetic form of dementia paralytica, with prolonged fluid normality, are possibilities with repeated courses of penicillin treatment alone. Tabetic pain may occasionally be given prolonged relief by use of penicillin, even in small total dosage, and always deserves a trial. In a small series of cases in which results of higher total dosage (9,600,000 units) were compared with those of lower total dosage (less than 4,800,000 units), the higher dosage seems to have some slight but not statistically established advantage. Though the authors adopted 9,000,000 units as their starting dosage, they did not feel that the superiority of the higher dosage was proved by their experience. A comparison of effects of around the clock administration of aqueous penicillin G with those of penicillin in oil and beeswax at 600,000 units given once daily in small series of patients with asymptomatic neurosyphilis (66 cases), at a total

dosage level of 4,800,000 units, showed practically no difference in fluid response in 120 days. If borne out for other retarder-penicillin combinations and longer observations, this would justify ambulatory treatment at least of asymptomatic neurosyphilis. A small pilot study of prepenicillin therapy of neurosyphilis (51 cases), including 76 per cent type 3 spinal fluids, is reviewed as background for the interpretation of penicillin effects. This study, to be continued into the coming year, suggests that absurdly little treatment with arsphenamine and bismuth alone may be effective and shows that without induction of malaria but with administration of tryparsamide® and typhoid vaccine (notably the former) normal and near normal fluids were obtained in 80 per cent of the patients in an observation period of two to 20 years. In this pilot study more than one-half the patients who achieved a normal or near normal fluid did so by the second year; 9 of 45 became normal later after a relapse through prolongation and intensification of treatment, and the spinal fluid of only six of 51 patients failed to become normal or near normal within the two to 20 year period. It is suggested that treatment with penicillin, like the older therapies, tips a balance between patient defense and disease offense and that the amount of treatment needed to accomplish this is not clearly predictable, even by the spinal fluid type. It varies from person to person and requires vigorous and prolonged observational control, including repeated spinal fluid examinations, for its estimation and the determination of course and outcome.

As a result of four years' study of 207 patients with various types of neurosyphilis (77 with asymptomatic neurosyphilis, 55 with dementia paralytica, 23 with tabes dorsalis, 17 with the tabetic form of dementia paralytica, 18 with meningovascular syphilis and 17 with miscellaneous forms), Callaway and his associates,[152] at Duke University, Durham, N. C., concluded that penicillin exerted a favorable influence in neurosyphilis. Penicillin alone in a dosage of 4,000,000 to 6,000,000 units is an effective agent in the treatment of all forms of syphilis of the central nervous system. Patients with symptomatic dementia paralytica responded best to penicillin therapy in this series, and the patients with congenital central nervous system syphilis responded most poorly. The patients with tabes dorsalis, the tabetic form of dementia paralytica and meningovascular syphilis responded equally well. It must be borne in mind that often severe organic damage to nonregenerable tissues has taken place in the patients with the tabetic form of dementia paralytica, tabes dorsalis and meningovascular syphilis, and complete return to normal cannot always be expected. Previously administered adequate chemotherapy does not appear to enhance the results obtained after penicillin therapy. Retreatment of neurosyphilitic patients seems to be of little value, unless there is definite evidence of failure of the protein content or cell count of the cerebrospinal fluid to return to normal limits or of relapse after approaching normal.

Nichols and Heyman [148a] reported their results in the treatment of 298 patients with asymptomatic neurosyphilis. One hundred and eighty-four of the patients showed a group 3 fluid, and 114 had fluids classified as group 2. Fifty-one patients received 2,400,000 to 3,000,000 units of amorphous penicillin; 89 patients received 4,000,000 units of amorphous penicillin; 78 received 4,800,000 units of

152. Callaway, J. L.; Flower, A. H.; Hirschmann, V. R., and Olansky, S.: A 4 Year Study of Penicillin Treatment of Syphilis of the Central Nervous System. South. M. J. **43**:412-422 (May) 1950.

crystalline penicillin G; 24 received 9,000,000 units of penicillin in oil and beeswax; 56 patients received 6,000,000 units of penicillin in oil and wax. Ten per cent of the entire series showed evidence of treatment failures, as indicated by a persistent elevation of the spinal fluid cell count six months or more following therapy. Eight (15.6 per cent) of the 51 patients treated with the smaller doses, i. e., 2,400,000 to 3,000,000 units of amorphous penicillin in aqueous solution, showed evidence of failure. The best spinal fluid response was obtained among the 78 patients treated with 4,800,000 units of crystalline penicillin G in aqueous solution. Only 5.1 per cent of cases in this group were classified as treatment failures. Ten per cent of the 56 patients treated with 6,000,000 units of penicillin in oil and wax have shown evidence of treatment failure. Of the 24 patients treated with 9,000,000 units of crystalline penicillin in oil and wax, 12.5 per cent had evidence of treatment failure. The percentage of patients obtaining normal spinal fluids was considerably greater among those with early syphilis of less than four years' duration (48.6 per cent) than among patients treated for late syphilis (16.1 per cent). Twenty-five per cent of the 114 patients with group 2 spinal fluids before treatment obtained a complete reversal of their spinal fluid findings, while only 16.8 per cent of the 184 patients who had maximal abnormalities obtained similar results. Eleven per cent of the patients in this series continued to show an increase in spinal fluid protein along with a positive Kolmer reaction, although the cell count became normal following treatment. The significance of the elevated spinal fluid protein in these cases is not known. Retreatment with larger doses of penicillin did not produce a significant decrease in the protein level. The incidence of therapeutic failure among patients treated with penicillin in oil and wax was slightly, but not significantly, greater than among those treated with comparable doses of penicillin in aqueous solution.

Evaluation of Treatment Procedures in Tabes Dorsalis.—Koteen [148b] describes some of the difficulties encountered in evaluation of treatment for tabes dorsalis. He states that the difficulties are due to the following factors: There is often an asymptomatic phase during which the patient may feel entirely well but may exhibit evidence of involvement of sensory tracts of the spinal cord with or without alteration of the cerebrospinal fluid. This period may extend from a few months to many years. Patients with tabes may complain of severe shooting pains and other symptoms without objective neurological changes. Spontaneous remissions and exacerbations are not uncommon. The role of reeducation in altering ataxia and urinary incontinence and the influence of psychic factors in the production and alleviation of lightning pains, gastric crisis and sexual impotency defy detailed analysis. The attitude of the interviewing physician may determine in part the response of the patient concerning interpretation of "improvement." The author studied 49 patients with tabes according to a preplanned experiment. The spinal fluids responded dramatically, and the improvement has been maintained with no evidence of spinal fluid relapse. Symptomatic response showed considerable variation. Only one of 11 previously untreated patients failed to obtain some relief from shooting pains. However, patients who previously failed to obtain relief from shooting pains after routine antisyphilitic therapy also were less likely to respond to penicillin. Fourteen patients who obtained either temporary or partial benefit from one course of penicillin were subsequently retreated, but only three were

appreciably aided by the second course of penicillin therapy. Five patients who were not benefited by one or more courses of penicillin underwent combined malaria and penicillin therapy. None of these patients reported elimination of pains. Previously untreated ataxic tabetics were greatly helped by penicillin. Previously treated patients, as a group, derived little benefit from a course of penicillin. Four of nine incontinent tabetics noted a decrease in their incontinence. Only one was definitely relieved of his symptoms. One of four patients with gastric crisis was apparently helped slightly by penicillin therapy. Two of seven impotent patients showed some improvement. Two patients with diplopia showed a prompt response to penicillin therapy. Penicillin had no effect on trophic lesions. Three patients acquired destructive joint disease following penicillin administration. The author bases his prognosis on three factors: (1) the nature of presenting signs and symptoms, (2) duration of these symptoms and (3) failure to respond to previous therapeutic measures. He states that the activity of the cerebrospinal fluid should not influence the decision whether or not to treat any patient and that the activity of the fluid is of little prognostic significance.

Treatment of Late Neurosyphilis with Penicillin: Clinical Failures.—Landau, Kopp, Rose and Solomon [149a] have treated 446 patients with neurosyphilis from February 1944 to March 1949. Three fourths of the patients had dementia paralytica. Penicillin was given in 3,000,000 or 6,000,000 unit dosage over intervals of five to 15 days. The majority of the patients were also given fever therapy, induced either by malaria or in a fever cabinet, in amounts equivalent to one-half the usually accepted treatment course. Seventy-two per cent of the neurosyphilitic patients followed one to five years are at home and at full working capacity. Fifty-two patients (12 per cent) died, but in only 16 could death be attributed to the syphilitic process. The adjusted mortality rate is 4 per cent. Seventeen patients (4 per cent) have been lost to follow-up. Analysis of the present clinical status of 233 paretic patients followed over one year indicates that the type of psychosis present prior to treatment is of value prognostically. Psychosis of the affective type has an excellent prognosis; all patients improved, although a few patients required electric shock therapy in addition to the penicillin. The demented group has a fair prognosis; 67 per cent of the patients improved. The schizophrenic-like group has the poorest prognosis; only 25 per cent improved. Analysis of the clinical failures on penicillin therapy reveals that the failure of the patients to improve is ascribable to either: (1) the type of psychosis present prior to treatment or (2) residuals of severe organic pathologic changes, or both. Of the 35 patients retreated for clinical considerations, 49 per cent are improved after one year of follow-up observation. Of the 20 patients retreated on the basis of persistence of cerebrospinal fluid abnormalities or relapse, 75 per cent are improved. All but a few of the unimproved group have dementia paralytica of the simple demented and schizophrenic-like types. The spinal fluid of all groups followed the usually reported improvement patterns. Of the 20 living patients who were given electric shock therapy in addition to treatment with penicillin and malaria, all the affective group are improved and at home, in contrast to the schizophrenic-like group, all of whom are unimproved and are hospitalized. These results are consistent with those usually found in the affective and schizophrenic psychoses without dementia paralytica. The results as a

whole suggest that the treatment used, namely, penicillin alone, penicillin with fever and repeated courses of both, brought an arrest of the pathological process to the patient followed a year or more. The lack of associated clinical improvement in some of these patients is due to neurological residuals of the disease and the type of psychosis present at the time of treatment.

Dattner [149b] found only 43 failures among 388 patients with active spinal fluid findings following an initial course of treatment with penicillin, varying in amount from 2,000,000 to 9,000,000 units, a failure rate of approximately 11 per cent of these 43; however, the disease in 24 responded favorably to a second course of penicillin, usually given in higher amounts than the first. Three patients of the group failed to respond even with repeated courses of penicillin therapy. One of these patients was a 27 year old Negro who had secondary syphilis with asymptomatic neurosyphilis. The other two had a symptomatic neurosyphilis. Dattner concluded that penicillin therapy for all types of neurosyphilis, if evaluated from the laboratory point of view, proved at least as effective as all previously used forms of treatment, and in his experience the same holds true for the clinical aspect.

TREATMENT OF SYPHILIS IN PREGNANCY

The value of penicillin treatment of syphilis in pregnancy is perhaps the least controversial phase of the subject of syphilotherapy. Sufficient experience has now been accumulated to allow certain more or less dogmatic statements which Ingraham and Beerman [153] have detailed. The factors responsible for the continued incidence of congenital syphilis have been delineated by Heyman and McCain [154] in a study which must be read in the original by all students of the problem. Individual reports, dealing with series of cases of various sizes, such as that of Hudson [155] and of Wammock and her co-workers,[156] indicate the favorable results of penicillin treatment of syphilis in the pregnant woman. Jones,[157] however, states that despite the use of penicillin in the treatment of syphilis in pregnancy a significant number of new cases of congenital infections has been discovered during the past several years.

Factors Responsible for Continued Incidence of Congenital Syphilis.—The continued occurrence of congenital syphilis prompted Heyman and McCain [154] to analyze the syphilitic infection and therapy in 77 mothers and infants with congenital syphilis treated at Grady Memorial Hospital in Atlanta, Ga., in the past four years. The presence of negative serologic reactions in pregnancy and inade-

153. Ingraham, N. R., Jr., and Beerman, H.: The Present Status of Penicillin in the Treatment of Syphilis in Pregnancy and Infantile Congenital Syphilis, Am. J. M. Sc. **219**:433-442 (April) 1950.

154. Heyman, A., and McCain, J. R.: Syphilis in Pregnancy: A Clinical Study of Factors Responsible for Congenital Syphilis, New England J. Med. **241**:960-964 (Dec. 15) 1949.

155. Hudson, D. V.: The Management of Syphilis in Pregnancy, J. Oklahoma M. A. **43**:153 (April) 1950.

156. Wammock, V. S.; Carrozzino, O. M.; Ingraham, N. R., Jr., and Clair, N. E.: Penicillin Therapy of Syphilitic Pregnant Woman: Its Practical Application to Large Urban Obstetrical Service, Am. J. Obst. & Gynec. **59**:806-819 (April) 1950.

157. Jones, R. W., Jr.: The Prevention of Congenital Syphilis, J. M. A. Georgia **39**:38 (Jan.) 1950.

quate arsenical therapy were responsible for congenital syphilis in two thirds of the infants. Factors responsible for the transmission of congenital syphilis were (1) failure of the clinic patients to come for antepartum care early in pregnancy, which accounted for one fourth of the cases; (2) inadequate therapy because antepartum care was late in pregnancy or patients were delinquent in treatment; (3) diagnosis late in pregnancy or antisyphilitic therapy which was not immediate or vigorous in a few cases; (4) neglect of private physicians to take serologic tests in a few instances; (5) negative serologic reactions in one fourth of the women for which reason antisyphilitic therapy was not given. These patients probably were in the incubation period or else acquired the infection late in pregnancy. The importance of repeated serologic tests is again emphasized. The duration of maternal infection was always less than five years prior to the birth of the syphilitic infant. The inadequacy of arsenical therapy given late in pregnancy is pointed out. Penicillin therapy is believed to be the treatment of choice and will probably reduce the incidence of congenital syphilis considerably.

Penicillin Therapy of Syphilis in Pregnancy and Infantile Congenital Syphilis.—Ingraham and Beerman [153] have brought up to date in a fully documented review the accepted and the controversial data regarding penicillin in the treatment of syphilis in pregnancy and infantile congenital syphilis. They discuss the following facts as reasonably well established in the treatment of the syphilitic pregnant woman with penicillin: 1. Penicillin readily permeates the human placenta. 2. Very small amounts of penicillin are often sufficient to prevent infection of the fetus in utero. 3. Larger doses of penicillin will result in almost 100 per cent nonsyphilitic infants, regardless of the stage of maternal syphilis treated. 4. Penicillin need not be supplemented by arsenic or bismuth. 5. Treatment reactions to penicillin have not proved to be serious and do not normally necessitate any modification of the treatment course. Ingraham and Beerman feel that the following points in the penicillin treatment of the syphilitic pregnant woman are still open to controversy or discussion: (1) the optimum treatment course (both optimum dosage and optimum duration of the treatment), (2) the addition of absorption-delaying vehicles to penicillin for ambulatory treatment and (3) retreatment in subsequent pregnancies. The facts in the penicillin treatment of infantile syphilis are less clearly established because of limitation of available case material. An optimum treatment course for infantile syphilis has not been established, but the common practices are described adequately and include, besides penicillin, (1) hospitalization, (2) pediatric care directed toward maintenance of proper fluid, salt and protein balance, (3) good nutrition and (4) the correction of existing anemia. This type of syphilis can be eliminated if present medical knowledge can be applied to the pregnant woman.

Penicillin Therapy for Pregnant Women with Syphilis.—Wammock and her associates [156] analyzed the results of penicillin therapy in 344 pregnant syphilitic women treated at the Philadelphia General Hospital since September 1946. A total of 2,400,000 Oxford units of aqueous penicillin (crystalline G) was given intramuscularly in 60 individual doses of 40,000 units each every three hours (7½ days). When penicillin was employed either before or during pregnancy, 94.5 per cent normal full term infants resulted and 1.7 per cent living syphilitic infants.

TREATMENT OF CONGENITAL SYPHILIS

Penicillin continues to offer the best means not only for prevention but for cure of congenital syphilis. Sufficient time has elapsed since the first patient was treated for the University of Pennsylvania group [158] to report on long term follow-up studies. Other series have also given uniformly good results.[159]

Long Term Follow-Up Study of Penicillin Therapy of Infantile Congenital Syphilis.—The carefully planned long term follow-up study by Rose, György and Ingraham [158] seems to bear out their previous impression of the remarkable superiority of treatment with penicillin in congenital infantile syphilis over all other previous therapeutic schemes and recommendations, not only with regard to the safety and relatively short duration of therapy but also in respect to the lack of clinical and serologic relapses. Sixty infants with congenital syphilis were treated with penicillin and followed for periods up to three years. Of the 48 living patients treated with penicillin intramuscularly, 37 were apparently cured (clinically well and with negative serologic reactions); seven were clinically well but still showed positive serologic reactions, with declining titer; three were well but revealed no change in titer. Five patients were treated with penicillin by mouth, four infants responding satisfactorily. One older child, 2⅓ years of age, responded well, but his serologic reaction remained positive after retreatment. The age of the patient at the onset of treatment, rather than the dosage, type or means of administration of penicillin, seemed to be the chief factor in determining satisfactory response; cures approached 100 per cent when treatment was commenced before the third month of life. The amounts of penicillin administered intramuscularly varied from 20,000 to 200,000 units per pound (44,000 to 440,000 units per kilogram) of body weight.

Penicillin Therapy of Congenital Syphilitic Nephrosis.—A case of congenital syphilitic nephrosis successfully treated with penicillin was reported by Scully and Yamazaki.[160]

TOXIC REACTIONS TO PENICILLIN

We have the impression from personal experience, as well as from the reports during the review period, that reactions to penicillin are on the increase. The cause for this is not clear but bears inquiry, since some of the reactions have proved fatal.

Nerve Injuries from Penicillin.—A new development this year was the reporting of the effects of penicillin on nerves and muscle.

Broadbent, Odom and Woodhall [161] report four cases of peripheral nerve injury following penicillin injection into or adjacent to major peripheral nerve trunks. The antibiotic-induced neuritis was characterized by intense immediate pain radiating distally along the course of the affected nerve segment, a complete, but in two cases

158. Rose, E. K.; György, P., and Ingraham, N. R., Jr.: Treatment of Congenital Syphilis: Results with Aqueous Penicillin Alone in 60 Infants Followed for an Average of 2 Years After Treatment, Am. J. Dis. Child. **77**:729-735 (June) 1949.

159. Thomas, E. W.: Rapid Treatment of Syphilis with Penicillin: II. Penicillin in Prenatal and Infantile Syphilis, Bull. World Health Organ. **2**:249-255, 1949. Morgan, E. A.: Penicillin in the Treatment of Pre-Natal Syphilis, Canad. M. A. J. **61**:275-278 (Sept.) 1949.

160. Scully, J. P., and Yamazaki, J. N.: Congenital Syphilitic Nephrosis Successfully Treated with Penicillin, Am. J. Dis. Child. **77**:652-658 (May) 1949.

161. Broadbent, T. R.; Odom, G. L., and Woodhall, B.: Nerve Injuries from Administration of Penicillin, J. A. M. A. **140**:1008-1010 (July 23) 1949.

rapidly regressing, sensory loss and an early motor disability that became a chronic and static disability in two instances. The reaction is unlike that produced by procaine anesthetization, and it appeared to be more intense when wax was used as a vehicle. Operative procedure in two cases suggested an intraneural lesion rather than an extraneural compression.

Matson [162] suggests, on the basis of experience with two cases, that early radical neurolysis may offer the best chance for maximum early recovery of function in cases of nerve injury from improper injection of an antibiotic (penicillin in oil and beeswax) into or adjacent to one of the major nerve trunks.

Dangers of Intrathecal Medication.—Wilson, Rupp and Wilson [163] present four case reports and a review of the literature of untoward reactions following intrathecal injections of anesthetics and penicillin. Peripheral and local neuropathy, encephalomyelitis, toxic psychosis, hemorrhagic encephalitis, paraplegia, cauda equina paralysis, radiculitis, arachnoiditis and aseptic meningitis have been reported after this mode of therapy. The neurotoxic action of penicillin has also been observed following large doses given intrathecally. The authors believe that if adequate spinal fluid concentrations of an agent can be obtained by systemic administration intrathecal administration is illogical and productive of permanent damage.

Black Hairy Tongue and Penicillin.—Although not entirely germane to the present treatment of syphilis, the use of penicillin lozenges has produced black hairy tongue.[164] Similar cases of black tongue as a result of administration of chloramphenicol (chloromycetin®) and aureomycin have been reported by Downing.[165]

Penicillin Hypersensitivity: Cutaneous.—Numerous studies on the cutaneous reactions to penicillin have appeared. Lepper and his co-workers [166] analyzed the incidence of allergic reactions in 1,303 patients receiving penicillin. Among 598 patients given aqueous crystalline penicillin the rate was 1.2 per cent; among 557 patients receiving crystalline penicillin in oil and beeswax it was 2.7 per cent, and among 148 patients administered procaine penicillin in oil it was 1.4 per cent. Local irritative reactions were more frequent and severer with penicillin in oil and beeswax than with aqueous crystalline penicillin or procaine penicillin in oil. This difference may be due to two factors: The penicillin is held in contact with the tissues in one site over a prolonged period, and in the same area as evidenced by the local irritation there are probably many damaged proteins which may conjugate with the penicillin and render it antigenic.

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162. Matson, D.: Early Neurolysis in the Treatment of Injury of the Peripheral Nerves Due to Faulty Injection of Antibiotics, New England J. Med. **242**:973-975 (June 22) 1950.

163. Wilson, G.; Rupp, C., and Wilson, W. W.: Dangers of Intrathecal Medication, J. A. M. A. **140**:1076-1079 (July 30) 1949.

164. Ayre, W. B.; Favreau, R., and Ayre, J. E.: Black Hairy Tongue Following Use of Penicillin, J. A. M. A. **141**:548 (Oct. 24) 1949. Wolfson, S. A.: Black Hairy Tongue Associated with Penicillin Therapy, ibid. **140**:1206-1208 (Aug. 13) 1949. Overman, W. E.: Penicillin and Black Hairy Tongue, Correspondence, ibid. **141**:1319 (Dec. 31) 1949.

165. Downing, J. G.: Black Tongue as a Result of Antibiotic Therapy, New England J. Med. **242**:1013 (June 29) 1950.

166. Lepper, M. H.; Dowling, H. F.; Robinson, J. A.; Stone, T. E.; Brickhouse, R. L.; Caldwell, E. R., Jr., and Whelton, R. L.: Studies on Hypersensitivity of Penicillin: I. Incidence of Reactions in 1,303 Patients, J. Clin. Investigation **28**:826-831 (Sept.) 1949.

Contact dermatitis was reported.[167] Samitz and Horvath [168] and Berne [169] cited examples of severe sensitivity reactions. Berne's case was fatal, with pathological lesions limited to the skin and gastrointestinal tract. Huber,[170] as well as Langdon,[171] reported examples of exfoliative dermatitis from use of penicillin.

Successful Desensitization to Penicillin.—Garai [172] reports on a patient with cardiovascular syphilis who had a pruritic bullous eruption following initial doses of crystalline sodium penicillin G. After the acute phase subsided, the patient's skin was tested with every available brand of sodium and potassium penicillin. Although skin tests gave positive reactions, calcium penicillin was best tolerated. The patient was desensitized with calcium penicillin with increasing doses given intradermally, then intracutaneously, several times daily. After the dosage reached 10,000 units three times a day without reaction, the patient was given 100,000 units a day for two weeks in fractional doses of 20,000 units each without untoward reactions.

Effect on Blood Clotting Activity in Human Beings.—In order to determine the effect of penicillin on the plotting activity of the blood, the clotting time, prothrombin time and heparin tolerance were determined by Dolkart and others [173] in 24 normal human subjects after intramuscular injection of 300,000 units of penicillin in beeswax and in four subjects after injection of 300,000 units of crystalline penicillin G in saline solution. No significant alterations in any of these values were noted; therefore, the authors concluded that penicillin G, administered in the usual therapeutic dosages, has no effect on the clotting activity of blood in normal human subjects. Quick [174] suggests that employment of his prothrombin consumption test may clarify the effects of antibiotics on blood coagulation.

Loeffler's Syndrome in Penicillin-Treated Patients.—Two cases of transitory pulmonary infiltrations associated with eosinophilia of peripheral blood (Loeffler's syndrome) are reported by Falk and Newcomer,[175] of the University of Pennsylvania, following intramuscular injections of penicillin in oil and wax for secondary syphilis. This syndrome of pulmonary infiltrate and eosinophilia is described as an allergic reaction occurring principally in persons with parasitic diseases. The

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167. Kile, R. L.: Contact Dermatitis from Procaine Penicillin, Arch. Dermat. & Syph. **61**:484 (March) 1950. Katzenstein, L.: Severe Contact Dermatitis of the Face Due to Nasal Inhalation of Penicillin Powder: Report of Case, Delaware State M. J. **21**:253 (Nov.) 1949. Peck, S. M., and Feldman, F. F.: Contact Allergic Dermatitis Due to the Procaine Fraction of Procaine Penicillin, J. Invest. Dermat. **13**:109-110 (Sept.) 1949.

168. Samitz, M. H., and Horvath, P. N.: Observations on Severe Penicillin Reactions, Ann. Allergy **7**:490 (July-Aug.) 1949.

169. Berne, R. M.: An Unusual Sensitivity Reaction to Penicillin: Report of a Case with Autopsy Findings, New England J. Med. **242**:814-817 (May 25) 1950.

170. Huber, T. E.: Exfoliative Dermatitis Due to Penicillin and Streptomycin, Mil. Surgeon **105**:4-6 (July) 1949.

171. Langdon, E.: Exfoliative Dermatitis Following the Administration of Penicillin, U. S. Armed Forces M. J. **1**:210-213 (Feb.) 1950.

172. Garai, F.: Successful Desensitization to Penicillin, J. A. M. A. **141**:25-26 (Sept. 3) 1949.

173. Dolkart, R. E.; Halpern, B.; Larkin, M.; Dey, F. L., and deTakats, G.: The Effect of Penicillin upon the Clotting Activity of Blood in Normal Human Subjects, J. Pharmacol. & Exper. Therap. **96**:291-294 (July) 1949.

174. Quick, A. J.: Antibiotics and Blood Coagulation, Correspondence, J. A. M. A. **142**: 505 (Feb. 18) 1950.

175. Falk, M. S., and Newcomer, V. D.: Loeffler's Syndrome: Occurrence in 2 Patients Treated with Penicillin in Oil and Wax, J. A. M. A. **141**:21-22 (Sept. 3) 1949.

syndrome varies in intensity and may be associated with fever, paroxysmal cough and moderate leukocytosis with eosinophilia of the blood and sputum, together with migratory pulmonary infiltrates, thereby simulating a pneumonic infection. Tests performed on the two patients incriminated the wax as the possible allergen.

Axelrod [176] reported a case of pulmonary embolism due to administration of penicillin in oil and wax and discussed the clinical features and differentiation from Loeffler's syndrome. He advised careful aspiration before injection of preparations of penicillin in oil. Miscellaneous reactions, anaphylactoid shock,[177] serum sickness [178] and questionable Shwartzman phenomenon [179] have also been reported.

Treatment of Penicillin Reactions.—Rouse [180] suggests the following scheme for prevention and treatment of severe penicillin and other drug reactions. Treatment is considered under two classifications: (1) that of a maculopapular erythematous rash with extreme itching, in which pruritus is controlled by use of antihistaminic drugs and the eruption is usually self limited, (2) and that of allergic reactions, which are controlled by adequate doses of the proper antihistaminic drug or drug combinations. General care of both groups of patients includes careful attention to the diet and elimination from the environment of all contact atopens to which they could be sensitive. Specific medication consists principally in the relief of presenting symptoms. Itching can generally be controlled by administration of diphenhydramine (benadryl®) hydrochloride or other antihistaminics. For sedation, chloral hydrate gives the most relaxation with the least side effect.

Occurrence of Jarisch-Herxheimer Reaction.—The so-called Herxheimer reaction continues to receive considerable attention. Fatalities attributed to therapeutic shock are now beginning to appear although the exact place of penicillin in their causation is not always definitive. Diefenback [181] reports a fatal Herxheimer reaction, with sudden aneurysmal dilatation and complete bronchial occlusion, following penicillin treatments. Shaffer and Shenkin [182] likewise report a fatal reaction in a patient with syphilitic pachyleptomeningitis.

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176. Axelrod, M.: Pulmonary Embolism Following Injection of Penicillin in Oil and Wax, J. A. M. A. **142**:802-804 (March 18) 1950.

177. Burleson, R. J.: Anaphylactoid Shock Due to Penicillin: Report of a Case, J. A. M. A. **142**:562-563 (Feb. 25) 1950.

178. Tunis, M. M.: Intravenous Procaine Hydrochloride Treatment of Penicillin Sensitivity Reaction Simulating Serum Sickness, Canad. M. A. J. **60**:289 (March) 1949. Felder, S. L., and Felder, L.: Unusual Reaction to Penicillin, J. A. M. A. **143**:361-362 (May 27) 1950. Kirsch, N.: Severe Allergic Reaction Following Penicillin, Connecticut M. J. **13**:1044-1047 (Nov.) 1949.

179. Boelter, M., and Hatoff, A.: The Shwartzman Phenomenon with Penicillin: Report of Case, Arch. Pediat. **66**:335-338 (Aug.) 1949.

180. Rouse, J. W. H.: Prevention and Treatment of Severe Penicillin and Other Drug Reactions, South. M. J. **43**:195-197 (March) 1950.

181. Diefenback, W. C. L.: Fatal Jarisch-Herxheimer Reaction with Sudden Aneurysmal Dilatation and Complete Bronchial Occlusion Following Penicillin Therapy, New England J. Med. **241**:95-96 (July 21) 1949.

182. Shaffer, B., and Shenkin, H. A.: Fatal Herxheimer Reaction Following Penicillin Therapy: Report of a Case of Syphilitic Pachyleptomeningitis, Am. J. Syph., Gonor. & Ven. Dis. **34**:78-82 (Jan.) 1950.

The following studies detail the observations of various authorities with regard to the Herxheimer reaction and its therapy: Bowen and his co-workers [183] reported 182 cases of syphilis complicating pregnancy. The reactions in the series were usually minimal, urticaria and febrile Herxheimer reactions. However, in two cases it was felt by Bowen and his associates that a serious reaction in the form of a placental or fetal Herxheimer reaction occurred. These resulted in premature labor and the delivery of a stillborn fetus. In each instance fetal movements and fetal heart tones were present before treatment was started and ceased within 24 hours after the institution of penicillin therapy. McDowell [184] performed peripheral blood studies in 17 patients with primary and secondary syphilis who were receiving penicillin therapy. Of the 17 patients 15 had febrile Jarisch-Herxheimer reactions within 10 hours after start of treatment. In 10 of the 15 patients there was a definite leukocytosis occurring before or at the same time as the temperature spike. The average increase in leukocytes was 89 per cent. Differential counts showed an increase in the polymorphonuclear series. There was also lymphopenia, with an average drop in the total lymphocyte count of 55 per cent. The causative factors in the leukocytosis and Jarisch-Herxheimer reaction are thought to be the same.

Herxheimer Reaction Due to Penicillin.—Putkonen and Rehtijärvi [185] studied the Herxheimer reaction in 257 patients with different forms of syphilis after administering to adults an initial dose of at least 100,000 units of penicillin and to children 500 to 3,000 units per kilogram of body weight. The intensity of the reaction was determined by recording the temperature hourly for one day. Among 16 patients with primary syphilis the febrile reaction failed to appear in only one; the maximum temperature was 39.2 C. (102.6 F.). In 55 patients with secondary syphilis the average maximal elevation was 38.2 C. (100.8 F.). In none of 46 patients with untreated latent syphilis did the temperature rise above 38 C. (100.4 F.), and in only five cases was the elevation above 37.5 C. (99.5 F.). No patient with cardiovascular syphilis had a febrile reaction of over 38 C. In a group of 57 patients with neurosyphilis the majority showed no febrile response. However, the reaction in dementia paralytica differed definitely from that in the other forms in that six of the 10 paretic patients had an elevation of temperature over 38 C. All except one of the 15 persons with early congenital syphilis showed a febrile reaction of the intensity described in acquired primary and secondary syphilis.

Diphenhydramine Therapy of Herxheimer Reaction.—Stewart [186] has shown that diphenhydramine hydrochloride has no effect in preventing or alleviating the Herxheimer reaction in early syphilitic patients treated with penicillin in oil and wax.

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183. Bowen, J. H.; Cole, H. N.; Driver, J. R.; Light, R. C., and Rauschkolb, J. E.: Herxheimer Reactions in Penicillin Treatment of Syphilis in Pregnancy, Arch. Dermat. & Syph. **58**:735-739 (Dec.) 1948.

184. McDowell, F.: Occurrence of a Transient Leucocytosis During the Jarisch-Herxheimer Reaction, Proc. Soc. Exper. Biol. & Med. **71**:568-569 (Aug.) 1949.

185. Putkonen, T., and Rehtijärvi, K.: Penicillin Causing Herxheimer Reaction in Syphilis, Duodecim **65**:423-441, 1949.

186. Stewart, J. J.: Effect of Diphenhydramine (Benadryl®) Hydrochloride on Herxheimer Reaction After Use of Penicillin, Arch. Dermat. & Syph. **60**:427-429 (Sept.) 1949.

TOXIC REACTIONS NOT DUE TO PENICILLIN

Brain Changes in Dogs Subjected to Hyperpyrexia.—Dobin and his coworkers [187] subjected 18 dogs to artificially induced hyperthermia of 107 F. for at least one hour and then studied the brains histologically. Eleven animals died shortly after or during the experiment. Seven lived for several months thereafter and with no apparent effect. Histologically, the brains of animals which died shortly after being subjected to hyperthermia demonstrated hyperemia, edema and an acute disease process of the parenchyma without signs of beginning repair. The brains of animals living for several months after subjection to hyperthermia demonstrated evidence of parenchymatous damage undergoing repair. Clinically, this group of animals showed no disturbance in motor function or behavior.

Dimercaprol Injection (BAL).—The usefulness of BAL in therapy of metallic poisoning is the subject of editorial comment in *The Journal of the American Medical Association.*[188] The only new report cited in this statement is that of Longcope and Luetscher,[189] who found BAL to be an effective antidote in the treatment of 59 of 61 patients with acute poisoning from mercury bichloride when the treatment was instituted within the first few hours after poisoning had occurred. In their well documented article Longcope and Luetscher review the story of BAL and the results of its use in the treatment of effects of metallic poisons (arsenic, mercury and gold). They list the following symptoms of poisoning by BAL: nausea and vomiting; headache; burning sensation of lips, mouth, etc.; feeling of constriction of throat, chest and hands; conjunctivitis, tearing and salivation; tingling of hands; burning sensation of penis; sweating of forehead and hands; abdominal pain; tremors and shakiness; pain in the lower part of the back, and elevation of blood pressure.

Treatment of Bismuth Stomatitis with BAL.—Reekie [190] reported the excellent result obtained in treating acute bismuth stomatitis with BAL. The stomatitis was produced by bismuth oxychloride administered to a 34 year old man in the treatment of his syphilis. Clinical response to BAL was evident almost from the first day of treatment, and improvement was continuous and rapid. By the tenth day the bismuth deposits and the blue lines had vanished.

Treatment of Arsphenamine Dermatitis with BAL.—Rouhunkoski [191] reported seven cases in which BAL was used to treat severe dermatitis produced by arsphenamine. The interval between the discovery of the dermatitis and the institution of treatment averaged 21 days. The period of treatment was prolonged,

187. Dobin, N. B.; Neymann, C. A., and Osborne, S. L.: Pathologic Changes in the Central Nervous System Resulting from Experimentally Produced Hyperpyrexia, J. Neuropath. & Exper. Neurol. **8**:295-304 (July) 1949.

188. BAL in the Treatment of Metallic Poisoning, editorial, J. A. M. A. **142**:488-489 (Feb. 18) 1950.

189. Longcope, W. T., and Luetscher, J. A., Jr.: The Use of BAL in the Treatment of the Injurious Effects of Arsenic, Mercury and Other Metallic Poisons, Ann. Int. Med. **31**:545-554 (Oct.) 1949.

190. Reekie, A. A. M.: Treatment of Bismuth Stomatitis with BAL, Brit. M. J. **2**:1213 (Nov. 26) 1949.

191. Rouhunkoski, S.: Dimercaptopropanol in Treatment of Salvarsan Dermatis (BAL), Duodecim **65**:475-485, 1949.

averaging 66 days. Rouhunkoski found it difficult to notice a convincing result of BAL therapy, and stressed the fact that early treatment was a prerequisite for its effectiveness.

Untoward Reaction to BAL.—Hagemann and Bagby [192] report on a patient with rheumatoid arthritis who acquired a gold dermatitis following the administration of 365 mg. of gold sodium thiomalate (myochrysine®). This rash faded appreciably during the first course of BAL therapy, only to relapse in several days. When BAL was readministered, a rash due to sensitivity to BAL developed which was far severer than the gold dermatitis. Sensitivity to gold sodium thiomalate and BAL was proved by positive patch test reactions in each instance.

Haynes and Ormond [193] report a case in which a patient with lichen planus eruption of the extremities had been cured by treatment with bismuth arsphenamine sulfonate (bismarsen®). Eight years later, when the eruption recurred, the patient had nonfatal acute thrombocytopenic purpura after the second dose of bismarsen.®

Icterus from Arsenicals.—The occurrence of jaundice during arsenical therapy is reported from the centers still using this type of preparation. Gennerich [194] has analyzed these cases of jaundice occurring among patients treated with arsphenamine at the German naval hospital at Kiel-Wik. During the period 1910 to 1915 there were no such cases among more than 2,500 patients, even though the amount of arsphenamine employed was large. Cases began to appear during World War I and increased in frequency and in severity until the end of that war. With the return of peace and improved nutrition of the people the epidemic ended. Hepatitis again increased during World War II, but to a lesser extent than previously, perhaps because the nutritional status of the German people did not deteriorate as much as formerly. The author concludes that arsphenamine plays no important role in the genesis of hepatitis occurring in patients with syphilis.

Reviewing the experiences of a syphilis clinic where syringes have been cleansed antiseptically since 1939 (prior to the increase in infectious hepatitis observed during World War II), Marcussen [195] points out that the incidence of infectious hepatitis has been comparable to that observed in diabetes clinics and among patients treated with pooled plasma. The frequency of hepatitis among syphilitic patients and among the general population of Copenhagen showed almost identical variations. There were decided seasonal fluctuations. It is assumed, therefore, that, although syringes may spread the virus of infectious hepatitis, the incidence of the clinical disease depends on seasonal variations in patient resistance.

György [196] presents additional evidence that the jaundice encountered during arsenical treatment is frequently due to an infectious agent rather than to the therapy itself. She notes that in Budapest the incidence of jaundice is high in certain

192. Hagemann, P. O., and Bagby, J. W.: Dermatitis Due to BAL (2,3-Dithiopropanol): A Complication in the Treatment of Gold Dermatitis, J. Missouri M. A. **46**:775 (Nov.) 1949.

193. Haynes, H. A., and Ormond, A. P.: Thrombopenic Purpura Due to Bismuth Arsphenamine Sulfonate (Bismarsen®), J. A. M. A. **142**:1066-1067 (April 8) 1950.

194. Gennerich, W.: Der Salvarsanikterus, Arch. f. Dermat. u. Syph. **188**:567-575 (Nov.) 1949.

195. Marcussen, P. V.: Hepatitis in a Venereological Clinic 1939-47, Acta dermat.-venereol. **29**:397-409, 1949.

196. György, E.: Nouvelles recherches sur les ictères au cours du traitement de la syphilis, Ann. de Dermat. et de Syph. **10**:150-152 (March-April) 1950.

clinics and low in others, that frequently there is a history of contact with jaundiced patients (or physicians), that animals have shown hepatitis following the injection of blood serum from patients with so-called arsenical jaundice and that there are cycles during which hepatitis occurs among patients of syphilis clinics.

Arsenical Therapy: Nitritoid Crisis.—Vámos [197] has reviewed the literature pertaining to the nitritoid crisis following the injection of arsphenamine compounds (arsenobenzols). In addition, he reports his own observation that a transient albuminuria is associated with this reaction. So constant was the finding that the author states that transient postinjection albuminuria, even in the absence of clinical symptoms, indicates that a nitritoid reaction has occurred. Even minor reactions of this type are considered to be of significance since if they are recognized subsequent and more serious reactions may be avoided.

The sudden transient albuminuria without cylindruria is interpreted by Vámos as evidence of the allergic origin of the nitritoid crisis. He and his co-workers [198] also have demonstrated that there are transitory increases in the serum proteins, especially in the globulin fraction, during this reaction. It is postulated that increased capillary permeability exists not only in the kidneys but throughout the body, similar to that which has been observed in anaphylactic shock. In cases of urticaria due to arsenicals, the increased capillary permeability appears to be limited to the skin.[199]

NEW ANTIBIOTICS

Terramycin.—As antibiotics are introduced, they are tried in treatment of syphilis. The latest to be investigated is terramycin. In a preliminary report on terramycin therapy of gonorrhea, granuloma inguinale and syphilis, Hendricks and others [200] used this drug in doses of 60 mg. per kilogram of body weight per day for eight days in six patients with dark field–positive primary and secondary lesions. The lesions were rendered dark field negative within 24 hours in one case, within 40 hours in a second and within 48 hours in the remaining four cases. Of the three cases with positive serologic reactions at the time of therapy, all three showed sero-reversal at the first post-treatment month. Terramycin causes disappearance of the causative organism in granuloma inguinale in three days, and healing is excellent. Using 1 Gm. of terramycin every six hours for two doses gave 100 per cent cure in cases of gonorrhea. Smaller dosages were less efficacious.

Aureomycin.—The application of aureomycin to syphilis therapy by the Mayo Clinic group continues, and O'Leary [201] and Kierland, Herrell and O'Leary [202]

197. Vámos, L.: Data on the Symptomatology, Diagnosis and Pathogenesis of the Nitritoid Crisis: Crisis Albuminurica Vámos, Acta dermat.-venereol. **29**:248-258, 1949.

198. Vámos, L.; Vértes, B., and Rácz, I.: Data on the Allergic Origin of the Nitritoid Crisis, Acta dermat.-venereol. **29**:233-239, 1949.

199. Vámos, L., and Rácz, S.: Clinical Similarity and Pathogenetic Difference Between the Arsenobenzol Urticaria and the Nitritoid Crisis, Acta dermat.-venereol. **29**:414-420, 1949.

200. Hendricks, F. D.; Greaves, A. B.; Olansky, S.; Taggart, S. R.; Lewis, C. N.; Landman, G. S.; MacDonald, G. R., and Welch, H.: Terramycin in the Treatment of Venereal Disease, J. A. M. A. **143**:4-5 (May 6) 1950.

201. O'Leary, P. A.: Treatment of Syphilis by Oral Use of Aureomycin, J. Oklahoma M. A. **42**:315-319 (Aug.) 1949.

202. Kierland, R. R.; Herrell, W. E., and O'Leary, P. A.: Treatment of Syphilis with Aureomycin Administered by Mouth, Arch. Dermat. & Syph. **61**:185-195 (Feb.) 1950.

have reported on its successful use orally in seven patients. Others have studied this preparation from the experimental and clinical standpoints. It has also been tried in yaws [203] and in pinta.[204] Wiggall and his associates [205] have shown that aureomycin therapy is effective in experimental rabbit and human syphilis. Using it in rabbits in total dosages of 50, 100 and 200 mg. per kilogram of body weight given intramuscularly at four hour intervals divided in three doses, they were able to demonstrate that aureomycin caused no appreciable diminution in the number of T. pallidum in subcutaneous syphilomas within the first 24 hours; within 48 hours there was a decrease of 50 to 90 per cent, and within 72 hours most of the lesions became dark field negative or contained only a few treponemes. Lesions healed in 10 days. They also used the drug in a protection test. Rabbits were inoculated intratesticularly with virulent T. pallidum and immediately treated with intramuscular injections of 12.5, 25 and 50 mg. per kilogram of body weight given twice daily for eight to 10 days. All the controls displayed orchitis, but none of the treated animals had clinical evidence of syphilis. Fifteen patients with primary and secondary syphilis were treated with 2 to 4 Gm. of aureomycin daily. Treponemes disappeared from the lesions in the same time as in the experimental animals. At the end of the study period the patients were treated with penicillin. The authors are opposed to the oral treatment of syphilis and are of the opinion that aureomycin should not be used for the treatment of syphilis until further experimental and clinical observations are made.

Levaditi and Vaisman [206] have studied the activity of aureomycin in experimental syphilitic infections of rabbits and mice. They confirm the results of other investigators who demonstrated that this antibiotic possesses definite treponemicidal action. Rabbits were treated orally over a period of five days with a total of 640 mg. per kilogram of body weight, and healing of all active lesions followed. Rabbits treated by intramuscular injections of aqueous or oily suspensions of aureomycin (400 to 1,500 mg. per kilogram) also were observed to become clinically cured, and popliteal lymph node transfers to normal animals were negative. Mice treated with aureomycin appeared to have been completely rid of the invading spirochetes. The authors suggest that the activity of aureomycin is somewhat less than that of penicillin or of arsenicals or bismuth preparations. This fact, together with the gastrointestinal upsets that frequently accompany its oral administration, suggests that aureomycin will not be used extensively in the routine therapy of syphilis.

Rodriquez and his associates [207] report on oral aureomycin therapy in 27 cases of early infectious (dark field–positive) syphilis. Twenty-one cases were of secondary and six of primary syphilis. The initial dose consisted of 2 Gm., repeated in four hours, followed by a maintenance dose of 1 Gm. every four hours for a total

203. Ampofo, O., and Findlay, G. M.: Aureomycin in the Treatment of Yaws and Tropical Ulcer in Africa, Nature, London **165**:398-399 (March 11) 1950.

204. Mazzotti, L., and Olarte, J.: Acción de la aureomicina en el mal del pinto, Rev. d. Inst. salub. y enferm. trop. **10**:219-221 (Sept.) 1949.

205. Wiggall, R. H.; Zheutlin, H. E. C.; Trice, E. R.; Elmendorf, D. F., Jr., and Robinson, R. C. V.: Studies on the Effect of Aureomycin on Treponema Pallidum, Am. J. Syph., Gonor. & Ven. Dis. **33**:416-423 (Sept.) 1949.

206. Levaditi, C., and Vaisman, A.: L'auréomycine: Nouvelle médication anti-syphilitique, Presse méd. **58**:333-334 (April) 1950.

207. Rodriquez, J.; Plotke, F.; Weinstein, S., and Harris, W. W.: Aureomycin and Its Effects in Early Stages of Syphilis, J. A. M. A. **141**:771-772 (Nov. 12) 1949.

of 70 Gm. Lesions became dark field negative in as little as 17 hours, but more frequently 65 hours, or an average of 39 hours, were required. Lesion healing was slower than after trivalent arsenical or penicillin therapy. Blood levels studied in seven cases showed a peak of concentration (2.63 micrograms per cubic centimeter of serum) at four hours. The level diminished gradually thereafter, ranging from 1.54 to 1.26 micrograms per cubic centimeter. Serologic response to treatment consisted of a definite trend toward negativity. A small percentage showed evidence of a febrile Herxheimer reactions. Nausea was alleviated by administration of aluminum hydroxide gel prior to each dose.

Willcox [208] treated nine patients with early syphilis (two with seronegative primary syphilis, two with seropositive primary syphilis, five with secondary syphilis) with aureomycin. The patients were Bantu Negroes in Southern Rhodesia. Willcox had a limited supply of aureomycin; so his treatment schedule was by necessity brief and inadequate. Each patient received aureomycin in doses of 750 to 1,500 mg. orally over 24 to 48 hours. Unfortunately, follow-up study was impossible. However, Willcox did know that one of his patients relapsed.

Irgang and Alexander [209] treated nine patients with early syphilis with aureomycin. In addition to oral administration of 2 to 4 Gm. a day in divided doses, they gave 20 mg. intramuscularly once or twice daily. They could not develop an optimum treatment schedule. Their conclusions were the same as those of O'Leary.[201]

Loomis [210] states that in a series of experiments on the specific inhibition of phosphorylation of nitrophenol it was observed that low concentrations of aureomycin consistently exhibited similar inhibitory activity. In this respect the action of aureomycin resembles that of dinitrophenol and other substituted phenols, as well as gramicidin, quinacrine hydrochloride (atabrine® dihydrochloride) and methylene blue. The test system employed is based on the enzymatic activity of normal metachloridine® (2-metanilamido 5-chloropyrimidine). The results suggest that the toxicity of aureomycin is derived from its ability to inhibit aerobic phosphorylation.

Reactions to Aureomycin.—Peck and Feldman [211] report three cases of allergic skin eruptions due to aureomycin, and Eichenlaub and Olivo [212] report herpes zoster and generalized papular eruption during oral administration of the antibiotic.

Antitreponemal Effect of Chloramphenicol.—In 1948 the treponemicidal action of chloramphenicol was reported by Smith and his associates,[213] after studies on experimentally induced syphilis in rabbits. After oral administration of 50 to 100

208. Willcox, R. R.: Aureomycin: A New Treatment for Syphilis? Brit. M. J. **2**:1076-1077 (Nov. 12) 1949; Some Modern Advances in the Treatment of Early Syphilis with Antibiotics, with Special Reference to Chloromycetin, Aureomycin and the "One Shot" Treatment with Penicillin, M. Press **222**:585-588 (Dec. 21) 1949.

209. Irgang, S., and Alexander, E. R.: Treatment of Early Syphilis with Aureomycin, Harlem Hosp. Bull. **1**:91-98 (Dec.) 1948.

210. Loomis, W. F.: On the Mechanism of Action of Aureomycin, Science **111**:474 (April 28) 1950.

211. Peck, S. M., and Feldman, F. F.: Sensitivity Reactions to Aureomycin, J. A. M. A. **142**:1137-1139 (April 15) 1950.

212. Eichenlaub, F. J., and Olivo, M. A.: Reactions to Aureomycin, Bull. Georgetown Univ. M. Center **3**:152 (Dec.-Jan.) 1949-1950.

213. Smith, R. M., and others: Chloromycetin: Biological Studies, J. Bact. **55**:425-477 (March) 1948.

mg. chloramphenicol per kilogram of body weight, the syphilitic lesions became temporarily free of spirochetes. With this dosage as a guide, Romansky and his associates,[214] of George Washington University and the Bureau of Venereal Disease, Washington, D. C., tested the therapeutic effects of the drug on 32 patients with early syphilis. Patients with lesions containing numerous T. pallida were selected for this study. One group of patients received a daily oral dose of 120 mg. per kilogram of body weight. This was given in six equally divided doses at four hour intervals and continued for six days. Other groups were given daily doses of 60 and 30 mg. per kilogram of body weight for four to eight days. With the 30 mg. dose spirochetes could not be demonstrated in the dark field examination by the end of 22 to 28 hours. Healing of the syphilitic lesions was recorded by the end of the four to eight day period. In a typical case the Eagle flocculation titer was reduced from 1 : 512 to 1 : 8 by the end of a three month convalescent period. The only toxic or untoward reactions noted with the selected doses were occasional mild diarrhea and dryness of the mouth. The Jarisch-Herxheimer reaction was less frequent and less severe than that observed in syphilitic patients treated with penicillin.

Chloramphenicol Treatment of Early Syphilis.—Robinson, Fox and Duvall[215] also treated 20 patients who had primary and secondary syphilis (dark field positive) with chloramphenicol and believed that long term studies must be carried out for final evaluation of this drug, but the necessity of giving multiple oral dosage will tend to make chloramphenicol of little value in the treatment of syphilis.

Willcox[216] briefly reports four cases of early syphilis treated with chloramphenicol with apparently good immediate results.

Placental Transfer of Chloramphenicol.—Scott and Warner[217] investigated the problem of whether or not chloramphenicol traversed the placental barrier. They administered 2 Gm. doses of the drug to 12 patients during term labor. Blood was collected at time of delivery from both the maternal and the fetal circulation. Colorimetric determinations revealed that 10 of the 12 patients had effective serum concentrations in the fetal cord blood within 71 minutes after the initial dose.

Ross and his associates[218] also studied this problem. After oral doses of 1 to 2 Gm. of chloramphenicol to 11 patients in active labor approximately one to five hours before delivery, the antibiotic was found to have passed the placental barrier in concentrations from 30 to 80 per cent of that noted in the maternal blood stream in six of the 11 patients. Probably a dose of 50 mg. per kilogram per 24 hours in four hour divided doses would assure in the majority of cases sufficient placental transmission of the drug to control susceptible infections in the infant.

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214. Romansky, M. J.: Olansky, S.; Taggart, S. R., and Robin, E. D.: Antitreponemal Effect of Chloramphenicol, Science **110**:639-640 (Dec. 9) 1949.

215. Robinson, R. C. V.; Fox, L. M., and Duvall, R. C.: Effect of Chloramphenicol in Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **33**:509-514 (Nov.) 1949. Robinson, H. M., and Robinson, H. M., Jr.: Studies on Chloramphenicol in Early Syphilis and Gonorrhea: Preliminary Report, South. M. J. **42**:988-991 (Nov.) 1949.

216. Willcox, R. R.: Chloramphenicol and the Venereal Diseases, Brit. M. J. **1**:467-468 (Feb. 25) 1950.

217. Scott, W. C., and Warner, R. F.: Placental Transfer of Chloramphenicol (Chloromycetin®), J. A. M. A. **142**:1331-1332 (April 29) 1950.

218. Ross, S.; Burke, F. G.; Sites, J.; Rice, E. C., and Washington, J. A.: Placental Transmission of Chloramphenicol (Chloromycetin®), J. A. M. A. **142**:1361 (April 29) 1950.

Chloramphenicol Reaction.—Volini and co-workers [219] report untoward reactions of the hemopoietic system attributed to chloramphenicol therapy. In three cases discussed the antibiotic was administered in therapeutic doses for typhoid (two) and for brucellosis. A severe reversible granulocytopenia appeared in the blood, and a granulocytic hypoplasia, with both erythroid and granulocytic maturation arrest, was found in the marrow.

ABORTIVE TREATMENT OF SYPHILIS

The prediagnostic treatment of syphilis has been mentioned above. In a sense this is a prophylactic procedure. Plotke and co-workers [220] report an investigation of the effectiveness of a single injection of penicillin in the prevention of infectious syphilis in persons exposed to it. This procedure was established at the venereal disease clinics of the Chicago Health Department from August 1947 to August 1948. Those included in the study were contacts whose exposure did not exceed three months and who had had no previous syphilitic infection or penicillin therapy of any kind. The reported contacts numbered 1,069, of which 927 failed to meet the criteria; the remainder, 142 subjects, constituted the study group. Of the 142 contacts, 65 were controls and were untreated. The remaining 75 patients received a single injection of 600,000 units of penicillin in beeswax and peanut oil. All subjects were followed serologically and clinically for six months. In the control group 15 patients, or 25.4 per cent, and in the treated group 3, or 4.3 per cent, displayed syphilis. Two of the three patients with failure in the treated group admitted reexposure, but one may assume there were reexposures in both series. In the control group the median number of 66 days elapsed between the date of last exposure and the date of the first symptoms of syphilis, whereas the corresponding period in the treated group was twice as long. Of the 1,069 contacts 233 were lost to follow-up. In the remaining 836 nearly 47 per cent, or 395, were found to be infected. It is concluded that contacts of patients having primary or secondary syphilis should be considered for prophylactic treatment if negative reactions are obtained on first examination. Such contacts should be given physical and serologic examinations monthly for six months.

A summary of the abortive treatment schedule of Alexander and co-workers [116] was given in the section on "Treatment in Early Syphilis."

PROPHYLAXIS

Circumcision.—As a basis for his well documented statistical report on the influence of circumcision on venereal disease, Hand [221] utilized the material in the venereal disease clinics of the United States Naval Hospital, St. Albans, N. Y. His study confirms the popular medical beliefs that (1) gonorrhea and syphilis are less common in the circumcised and (2) chancroid is rare in the circumcised. Hand also concluded that lymphogranuloma venereum is almost never seen in the circumcised.

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219. Volini, I. F.; Greenspan, I.; Ehrlich, L.; Gonner, J. A.; Felsenfeld, O., and Schwartz S. O.: Hemopoietic Changes During Administration of Chloramphenicol (Chloromycetin®), J. A. M. A. **142**:1333-1335 (April 29) 1950.

220. Plotke, F.; Eisenberg, H.; Baker, A. H., and Laughlin, M. E.: Penicillin in the Abortive Treatment of Syphilis, J. Ven. Dis. Inform. **30**:252-256 (Sept.) 1949.

221. Hand, E. A.: Circumcision and Venereal Disease, Arch. Dermat. & Syph. **60**:341-346 (Sept.) 1949.

SYPHILIS AND OTHER DISEASES (INCLUDING SYPHILOID DISEASES)

Yaws.—Hackett [222] has pointed out certain aspects of yaws that require further investigation. The relationships between syphilis and yaws are vague and imperfectly understood, and because of the great differences of opinion among various authorities the author suggests that a precise decision on the question of identity must await studies of the antigenic properties of the different organisms. The epidemiological aspects of yaws also require further clarification, especially so far as the role of insects in the spread of the disease is concerned. Other gaps in the knowledge of yaws include correlation of the incidence of the disease with climatic factors and living conditions; the pathological aspects of early yaws and the distribution of the organisms throughout the body; the problem of the extent to which yaws may involve the central nervous system and the cardiovascular apparatus; the question of whether the fetus may be infected in utero; development of a serologic test that will differentiate yaws from syphilis, and the need for more suitable schemes of therapy.

Guimarães [223] has detailed certain considerations he believes to be essential to a yaws eradication campaign. He stresses particularly the desirability of administering treatment under hospital (or "lodgment") conditions because of the difficulties of persuading members of the rural populations to return for repeated injections. Pointing out that yaws is by no means a benign disease, he recommends multiple injections of penicillin in amounts comparable to those used in the treatment of early syphilis. The value of health education of the public and the necessity of long-continued community programs are indicated.

Guimarães,[224] working at the Oswaldo Cruz Institute in Brazil, has recorded his experiences with the use of procaine penicillin in the treatment of 30 patients with yaws. Injections were given every other day over a five day period, the total amount of penicillin administered being 36,000 units per kilogram of body weight. In all cases treponemes disappeared from the open lesions within 24 hours and in some cases more rapidly. Twenty-eight of the patients (93.3 per cent) remained clinically cured, and 18 (60 per cent) were observed to have serologically negative reactions within one year.

Relationship Between Yaws and Pinta.—Gonçalves [225] subscribes to the view that yaws and pinta are distinct diseases, each caused by a different species of treponeme. His reports give full and well documented details for his contention.

Bejel: Comparison with Syphilis and Control Measures.—Akrawi,[226] of the Royal College of Medicine, Baghdad, Iraq, attempts to answer three main questions involved in the problem of bejel: 1. Is bejel syphilis? 2. What is the method of transmission? 3. Why does bejel, if it is syphilis, take in some respects a different course from the latter? Although the clinical facts are brought out by this

222. Hackett, C. J.: Gaps in the Knowledge of Yaws, Tr. Roy. Soc. Trop. Med. & Hyg. **43**:311-316 (Nov.) 1949.

223. Guimarães, F. N.: Bouba: Consideraçãoes sôbre seu tratamento e profilaxia a "albergagem" como base das campanhas preventivas, O Hospital **37**:275-282 (Feb.) 1950.

224. Guimarães, F. N.: Experiências com altos doses de penicilina-procaínica no tratamento da bouba (framboésia, pian, yaws), O Hospital **37**:361-369 (March) 1950.

225. Gonçalves, A. P.: Relaçãoes entre a bouba e a pinta, An. brasil. de dermat. e sif. **25**: 1-15 (March) 1950.

226. Akrawi, F.: Is Bejel Syphilis? Brit. J. Ven. Dis. **25**:115-123 (Sept.) 1949.

study, it is not possible to answer any of these questions. The conclusions reached are that bejel is a widespread spirochetosis among certain tribes of the Middle East. It differs from syphilis mainly in the absence of a primary sore, in the predominance of the mucous patch in the early stages and the gumma of the palate in the later stages and in its nonvenereal mode of infection among children in most cases. The identity of bejel and syphilis is proved by the coinciding clinical symptomatology, the existence of congenital bejel (but with some explainable variation as compared with syphilis), the presence of meningovascular manifestations in both diseases, the failure to infect persons having dementia paralytica with bejel, the experimental reproduction of a primary sore in nonsyphilitic volunteers and the identity of their bacteriologic and histopathological aspects. The differences between the clinical aspects of bejel and those of syphilis are fully discussed, and an attempt is made to explain them on both theoretical and experimental grounds. Transmission through drinking water with a common vessel and through flies (mechanical vectors) is proved. B_2 avitaminosis, streptococcic rhagades and fissures and the severity of the climate also probably play a role. Since the epidemiology of bejel differs from that of syphilis, the ideal method of attacking the disease is the improvement of the hygienic conditions of the tribes by an extensive land settlement scheme. However, in the circumstances prevailing in Iraq the greatest difficulties stand in the way of such a solution, and these may continue for many years to come. The same can be said of the possibility of treatment of the individual person on the same lines as the treatment of syphilis because no government in the Middle East can bear the expenses of such a campaign. To every observer of bejel it is obvious that the mucous patch is the main source of this widespread infection. The present ambulatory dispensaries, while carrying on the fight against other endemic diseases, such as malaria and ancylostomiasis, can look for persons with mucous patches and treat them symptomatically with a few injections of one or more of the antisyphilitic drugs.

Lymphogranuloma Venereum and Syphilis.—Rávnay [227] studied the question of whether there is any connection between syphilis and lymphogranuloma venereum such that one disease might predispose to the other. At the Szeged Clinic, Szeged, Hungary, there were 36 cases of lymphogranuloma venereum, in 15 of which syphilis was also diagnosed. In five cases there was probably simultaneous double infection; in eight cases the syphilis was contracted first, and in two instances the patients with lymphogranuloma venereum later contracted syphilis. Rávnay could not demonstrate any direct connection between these two diseases.

Pernicious Anemia Complicated by Syphilis.—Zimon and LeRoy [228] describe three patients with pernicious anemia complicated by syphilis. They maintain that penicillin can be administered rapidly with safety and benefit to patients with pernicious anemia complicated by the late phases of syphilis. Early treatment even facilitates erythropoietic response.

Syphilis and Tuberculosis.—Certain dermatoses, notably small follicular papular syphilids, have been considered by some dermatologists to be the result of con-

227. Rávnay, T.: Lymphogranuloma inguinale und Syphilis, Dermatologica **98**:144-149, 1949.

228. Zimon, Z., and LeRoy, G. V.: Pernicious Anemia Complicated by Syphilis: Report of 3 Cases, Am. J. M. Sc. **218**:179-185 (Aug.) 1949.

comitant skin tuberculosis and syphilis. Greither [229] has studied 10 such cases clinically and histopathologically and reports that, although two of his patients had overt tuberculosis, there was no demonstrable association between the two diseases in the dermal lesions, which were entirely syphilitic. In his hands the Moro test gave no helpful information. The origin of this type of follicular papular lesion appears to be a combination of syphilitic infection and anomalies of cornification in the form of keratosis follicularis.

Herpes Simplex and Syphilis.—Blum and Collart [230] have so frequently observed genital or extragenital herpes during the incubation period of syphilis that they recommend clinical and serologic studies over a period of 60 to 90 days on all patients with herpetic lesions in order that coexistent syphilitic infections may be excluded or detected early.

CONTROL OF SYPHILIS

Decrease in Reporting as a Factor in the Incidence of Syphilis.—According to Bauer [231] the reported civilian rate of primary and secondary syphilis in the United States is the lowest since reporting by stage began in 1941. The rate in June 1949 had dropped 50 per cent from the peak of incidence in the second quarter of 1947 and is now 15 per 1,000. The discovery rate of early latent syphilis has also decreased slightly and lends its support to the premise of diminished incidence. The fact that case finding and contact investigation continue at the same rate further substantiates the thesis of decreased incidence. The widespread use of penicillin for gonorrhea and nonvenereal conditions may mask or alter symptoms. However, the low incidence of penicillin-masked syphilis in cases of gonorrhea and the decrease in discovery of latent syphilis cannot account for all the decrease in primary and secondary syphilis. A special case finding project in a Mississippi county from September 1947 to June 1948 showed an increase of 100 per cent in incidence of primary and secondary syphilis above that of a previous year, whereas a similar county without a special program reported a 50 per cent decrease, or the same as the national rate. Therefore, in some areas without case-finding methods syphilis continues to go undetected and untreated, while in others effective control measures are functioning. The problem of finding the "undiscovered" cases continues to face the venereal disease control officers.

This same decline was noted in New York.[232] The decrease in the number of case reports for early syphilis, which began in 1947, continued in 1948, 1,236 cases being so diagnosed in 1948 compared with 1,970 in 1947 and 3,063 in 1946, the peak year. About 48 per cent of these cases were of Negroes, who make up about 3 per cent of the upstate population. Incidence of late syphilis also continued to decline, with 3,992 cases (newly discovered) reported, the lowest since the

229. Greither, A.: Kleinpapulöse Syphilide und Mororeaktion: Ein Beitrag zur Frage der Beziehungen zwischen Syphilis und Tuberkulose sowie zum Formenkreis der follikulären Hyperkeratosen, Arch. f. Dermat. u. Syph. **188**:584-632 (Nov.) 1949.

230. Blum, P., and Collart, P.: La syphilis pré-chancreuse; diagnostic et traitement ultra-précoces, Arch. belges dermat. et syph. **5**:305-306 (Dec.) 1949.

231. Bauer, T. J.: Is the Incidence of Syphilis Decreasing? editorial, J. Ven. Dis. Inform. **30**:185-186 (July) 1949. Federal Security Agency: Cases of Acquired Syphilis Reported by States and Territories, Fiscal Year Quarters 1941 to Date, ibid. **30**:209, 1949.

232. Early Syphilis Case Reports Continue Decline in 1948, New York State Dept. Health Bull. **2**:51-52 (Aug. 8) 1949.

reporting system was instituted in 1936. The question is raised whether or not this decrease in reported early syphilis means an actual reduction in the incidence in New York state, since the report measures discovery, not incidence. However, one may conclude that, weighing all factors involved, the decline in syphilis in New York state is a real one.

Untreated Syphilis in the Male Negro.—Pesare, Bauer and Gleeson [38] in a comparative study of syphilis in treated and untreated Negro men present their findings for an observation period of 16 years. Further details of this study are given in the section on "Prognosis."

Third Session of the Expert Committee on Venereal Infections.—The World Health Organization Expert Committee on Venereal Infections [233] met for its third session in Washington, D. C., in October 1949. The committee discussed control technics, antibiotic therapy in syphilis and other treponematoses and serologic and laboratory aspects of venereal infections. The success of penicillin therapy in eradication projects against yaws and syphilis in parts of Africa has encouraged the World Health Organization to support a similar campaign against yaws in the island of Haiti. The committee recommended the use of procaine penicillin G in oil with 2 per cent aluminum monostearate in this project. Another project to gain support is that of the identification of bejel as an endemic syphilitic disease. The bejel project in the Eastern Mediterranean will be carried out by a special team of three or four experts to explore the epidemiological, clinical and laboratory aspects of bejel. Disease eradication based on penicillin treatment and case-finding technics could be carried out. Concomitant with the control program would be comparative laboratory studies, particularly on treponemes of syphilis and bejel.

Psychiatric Implications of Venereal Disease.—In delineating the psychopathological implications of venereal diseases, Pahmer [234] states that the basic problem is caused by the splitting of the physical aspects of sexuality from the emotional, affective life of the person. He maintains that as long as this dichotomy is not recognized no completely successful program of venereal disease control can be carried out. In his discussion of the emotional impact with which the venereally infected patient meets his infection, several unsolved problems are suggested for future investigators. Even for the nonanalytically oriented psychiatrist it is difficult to find a more fruitful territory for the exploration of unconscious masochistic wishes than in the exposure to venereal disease and the psychological reactions to venereal infection. This is particularly true of those patients who contract venereal disease despite all indoctrination, previous experience or pain in a monotonously repetitive manner. For practical purposes and because of their social implications, the attitudes of revenge and "getting even" found in so many patients deserve critical attention. These hostile, aggressive tendencies are not caused by the disease itself, but may erupt under various forms at the time of the discovery of the infection. For some retaliation will take the form of refusal to disclose the whereabouts of the infecting partner, who will then continue to

233. New Developments in Venereal Disease Control, Chron. World Health Organ. **4**:35-40 (Feb.) 1950.

234. Pahmer, M.: Psychiatric Implications of Venereal Disease: An American Survey, Brit. J. Ven. Dis. **25**:124-132 (Sept.) 1949.

evade treatment and, therefore, contaminate others or suffer the ill effects of untreated infection. For others, homicidal assault of the partner will sometimes result from a pent-up resentment. Still others will deliberately expose uninfected partners, applying the law of retaliation in its sadistic inhumanity. It is particularly interesting, in the light of Pahmer's psychological formulation of promiscuity, to emphasize the following points. Promiscuous intercourse is a one-sided physical experience between human beings in which one of the partners totally disregards the needs, integrity and self esteem of the other as a person, doing so for purposes dictated by narcissistic self love, reassurance against fears of rejection or attraction to one's own sex and anxiety concerning one's competence and normality in matters sexual or otherwise. In many cases it also represents discharge of aggressive impulses in what amounts to sexual assault, depreciation and reviling of the partner, punishment for real or phantasied guilt, adherence to infantile forms of eroticism by means of a partner of the opposite sex and crudely disguised, insurmountable early attachments and identifications. In other words instead of the free, genuine, spontaneous interplay and exchange of sexual and emotional currents of mature partners, sexual promiscuity is a monotonous and repetitive physical compulsion without real pleasure, lacking any permanency or constructive aspect and carrying its inherent punishment in the form of venereal infection. Pahmer concludes his fascinating analytic discussion with the familiar quotation from Freud: "In the last resort, we must begin to love in order that we may not fall ill, and we must fall ill if, in consequence of frustration, we cannot love."

Geiger and his co-workers [235] report on the demonstration of the application of psychotherapy and psychiatric case work to promiscuity undertaken by the San Francisco Department of Public Health with funds granted by the United States Public Health Service. A special service known as the Psychiatric Service of the San Francisco City Clinic was made a part of the venereal disease clinic to study and treat promiscuous and potentially promiscuous girls and men. The six year study revealed sexual promiscuity to be a problem in interpersonal relationships, namely, broken homes, and conflicts, inadequacies or disorganization within the personality. Environment, although contributing to promiscuous behavior, could not be considered as the primary cause in any case of habitual promiscuity. It was demonstrated that select patients could utilize treatment to modify their sexual behavior. Of 67 women patients who utilized continuing treatment, follow-up data were secured on 46 (69 per cent). Of this number 42 (91 per cent) had either reduced or ceased their promiscuity or, if potentially promiscuous, had not become promiscuous.

Attitudes of Patients to Clinics and Treatment Centers.—Usilton and Morse [236] describe a study in which 1,700 persons in clinics and rapid treatment centers in seven states were questioned to determine their attitudes to these facilities. In general, the attitudes of patients to clinics and treatment centers are quite favorable. There were differences in opinions of patients from clinic to clinic, thus indicating

235. Geiger, J. C.; Koch, R. A.; Safier, B., and Corrigan, H.: Psychiatric Approach to Promiscuity: San Francisco City Clinic Demonstrates Application of Psychiatry to Promiscuity in Venereal Disease Control, Health News, Albany **26**:3-5 (Aug.) 1949.

236. Usilton, L. J., and Morse, J. W.: Attitude of Venereal Disease Patients Toward Clinics and Rapid Treatment Centers, J. Ven. Dis. Inform. **30**:275-280 (Oct.) 1949.

possibilities of improvement. The patients in the youngest age group in both clinics and centers were about four times as unfavorable as those patients in the oldest age group. This finding is not desirable, and good favor should be insured in the younger group in which early syphilis is more prevalent. Eight per cent of clinic patients stated they would not recommend the clinic to persons needing examination for venereal disease. About 4 per cent of the treatment center patients said they would not recommend the center. Word of mouth advice is an important factor in getting infected persons to seek diagnosis; holding conditions for criticism to a minimum and creating favorable attitudes are important from the case-finding point of view. The main criticism of the clinic patient was directed to long waiting periods and objection to "needles" or "shots" whereas the criticism of rapid treatment centers were directed to the food, treatment and miscellaneous conditions, as lack of reading facilities.

Individual and Social Factors in Venereal Disease.—In a comprehensive survey Sutherland [237] covers the subject of individual and social factors in venereal disease under the following headings: incidence of venereal disease; characteristics of the promiscuous person, age, sex, intelligence, education, religion, marital status, socioeconomic status, residence, family background, personality, meeting place and effects of war; reason for promiscuity; reaction to infection; motivation for going to clinic; regularity of attendance, rehabilitation, and sex education. The author concludes that there is no such thing as an average venereal disease patient, but that certain individual and social factors tend to be associated with promiscuity in venereal disease. In the therapy of venereal disease it is necessary to study and treat the whole patient, and fears and anxieties must be uncovered and allayed. The patient must be treated as a disturbed personality, as well as a diseased body. In the person who acquired a venereal disease on his first exposure, the evidence collected by the author suggests that the behavior in the majority of cases which led to the infection was an expression of serious disturbance within the person or between him and the civilization in which he lives, the conventions and the moral codes that society demands he serve. In this light the venereal disease is a symptom rather than a closed entity—an expression of internal or external emotional maladjustment and disharmony. It is true that with modern methods of treatment in the great majority of instances the patient can be cured of his venereal disease. But unless we probe to find out what the factors are within him or in his environment that have brought him to this pass and unless, having found these factors, we directly or through other agencies help him to overcome the external difficulties and to modify his reaction to them we are merely sending back into sexual circulation someone who is fundamentally unchanged and who is likely to expose himself and others to infection again. In short, we have only temporarily broken the chain of infection. The results of the San Francisco attempts at rehabilitation suggest that this is a field that might with advantage be developed in England. Venereal disease is in many cases a symptom of promiscuous habits which, in a society that ostensibly puts sexual morality so high in its moral code, suggests that there are internal or external contributing factors in some degree peculiar to the person concerned. We must, therefore, increase the study and extend the knowledge of

237. Sutherland, R.: Some Individual and Social Factors in Venereal Disease, Brit. J. Ven. Dis. **26**:1-15 (March) 1950.

these individual and social factors that lie behind the problem of venereal disease and promiscuity. The author is convinced that workers in England have not yet to any great degree applied the sociomedical approach to the study of venereal disease.

Contact Investigation in Syphilis.—Bauer [238] states that contact investigation discovers 25 per cent of primary and secondary syphilis, 29 per cent of early latent syphilis, 25 per cent of congenital syphilis and 18 per cent of late syphilis now diagnosed in the entire United States. For every two contacts of early syphilis a new case of syphilis is diagnosed. In contrast, among every 20 persons seeking diagnosis on their own initiative there is only one new case of syphilis. Within the past four years the number of contacts reported has increased 51 per cent on a "per patient" basis; the number of contacts identified as infected was 62 per cent; the number brought to treatment was 94 per cent and the number of new cases of syphilis with open lesions 89 per cent. These figures show a remarkable progress in the efficiency of contact investigation procedure. Bauer stresses the importance of familial contact investigation in detection and prevention of congenital syphilis.

Value of Epidemiological Methods.—In a study conducted by the Chicago Venereal Disease Control Program during a three month period (1948) in order to determine the most effective epidemiological policy in investigating 280 persons having positive serologic reactions, Plotke and his co-workers [239] concluded that the best policy for tracing such persons is the initial letter, with field investigation done on those persons who fail to respond. Field investigation in cases in which the letter is returned unclaimed is of no value. By investigation of all persons 35 years of age and under with positive serologic reactions, the majority of infectious suspects can be detected. Lastly, all persons with positive serologic reactions should be notified to report to their private physician or health department.

Factors Affecting the Results of Contact Interviewing.—Rion and Abraham [240] report on a study which was made in 10 states between September 1946 and December 1947 of the number of contacts named by 1,968 patients with primary or secondary syphilis (461 white men, 318 white women, 608 Negro men, and 581 Negro women). They wanted to discover whether the variations in contact indexes are associated with factors over which the health department can exercise control or whether the variations were associated with differences in the types of patients available for interview. Analysis of the data collected revealed that interviewing differences were the main source of variation, rather than differences in the type of patient available for interview.

Technic for Contact Identification.—Fiumara [241] attempts to describe in detail the type of information necessary for the identification of a contact. For this

238. Bauer, T. J.: Contact Investigation of Syphilis, J. Ven. Dis. Inform. **30**:339-340 (Dec.) 1949.

239. Plotke, F.; Baker, A. H.; Fishtein, R. G.; Laughlin, M. E., and Schreiner, G.: Evaluating Epidemiologic Policy: Illustrated by an Analysis of Current Epidemiologic Policy on Field Investigation of Positive Blood Reports, J. Ven. Dis. Inform. **31**:76-79 (March) 1950.

240. Rion, J. W., and Abraham, S.: Factors Affecting the Results of Interviewing of Contacts, J. Ven. Dis. Inform. **30**:341-347 (Dec.) 1949.

241. Fiumara, N. J.: Describing a Contact of Venereal Disease, Am. J. Syph., Gonor. & Ven. Dis. **33**:380-388 (July) 1949.

purpose the epidemiological report form has been utilized to serve as a guide for the interviewer in obtaining the minimum of contact information. A supplemental questionnaire was introduced and should be used whenever inadequate contact information is obtained during a routine interview. Repeated interviews are a *sine qua non* for successful contact identification.

According to Holmes and his co-workers,[242] the Department of Public Health of Richmond, Va., is now conducting a multiphasic screening program, hoping to test some 60,000 persons within a six month period for the following conditions: syphilis, tuberculosis, other diseases of the chest, heart disease, hypertension, anemia, diabetes, obesity, disorders in visual acuity and intraocular tension. Every tenth person will have an electrocardiogram with 12 leads as a special study, as well as visual acuity tests. Every third person is offered an intraocular tension test. The clinics were first in large department stores. Twelve thousand persons were screened in the first 28 days. Later, the clinics will move to neighborhood and industrial areas, preceded by promotional work suitable for the new sites. The full term staff consists of 29 employees, 22 of whom work in the clinic proper. Each is assigned to handle at least two assignments, three are laboratory workers and four are assigned to the record room. Other workers consist of registered nurses Red Cross volunteers and typists. The flow of persons through the multitest clinic is handled differently. Between 60 to 70 persons an hour are screened. The actual screening time ranges from 13 to 15 minutes. The entire cost, including allowance for consultation service, will probably be $1.62. Previous serologic surveys cost over $1 per person. Therefore, this method is most economical. The results of the laboratory tests are followed up by the private physician of the patient's choice, who will interpret findings and advise or treat the patient accordingly.

Evaluation of Case-Finding Measures in Multiple Episodes of Infectious Syphilis.—Wright and Sheps discussed the importance of careful evaluation of the effectiveness of various case-finding measures in newly discovered cases of syphilis in a previous paper. This report [243] is a similar analysis of 142 cases of infectious syphilis due to relapse or reinfection occurring in patients who had been previously treated for syphilis, who had received a measure of venereal disease education and who had visible lesions at the time of diagnosis. All the patients in this study were Negroes. The low incidence of reinfection or relapse in white patients was not sufficient to consider studying. In terms of relative effectiveness of various case-finding measures, the problem of discovering and bringing under control those persons who have multiple episodes of infectious syphilis is essentially the same as that of discovering first infections. Of 142 cases, 41.5 per cent of the patients came in on their own initiative (42.1 per cent reported the original infection on their own initiative in a previous study). Special field efforts were most effective in the female patients, bringing to diagnosis 49.4 per cent of the total female group. In the males the educational process was the most important case-finding measure, being responsible for 57.1 per cent of the male cases. Special field efforts located

242. Holmes, E. M., Jr.; Bowden, P. W., and Stone, J. H.: Mass Screen Testing, J. Ven. Dis. Inform. **31**:151-155 (June) 1950.

243. Wright, J. J., and Sheps, C. G.: Reports of the North Carolina Syphilitic Studies: II. An Evaluation of Case-Finding Measures in Multiple Episodes of Infectious Syphilis, J. Ven. Dis. Inform. **30**:187-194 (July) 1949.

38.1 per cent. Only 29.1 per cent of female patients reported on their own initiative. This suggests that education aimed at raising the "level of suspicion" of the lay person is not reaching the females or that they ascribe visible lesions to other causes. The fact that a patient comes for diagnosis on his own initiative at the time of previous syphilitic episodes is not a reliable index that he will appear for subsequent episodes, despite visibility of the lesions, was also proved in this study. The data seem to indicate quite strongly that if special effects in contact tracing and follow-up on lapsed cases are relaxed in a health department, and reliance is placed on educational effort alone, many of the cases of multiple episodes of infectious syphilis may escape detection.

Mass Public Venereal Disease Education: Ohio Fairs.—Freeble and his co-workers [244] report that the Ohio Department of Health, in collaboration with local health authorities, sponsored an educational exhibit which invaded the midways of eight county fairs and one state fair in Ohio in 1948. The exhibit attracted 119,783 persons. Free literature and movies presented in a casual manner seemed to be the secret of its success. No restrictions of age, sex or race were made. There were no questionnaires to fill out, nor were there any lectures. Remarks of visitors show the desire for such information. The Venereal Disease Division has already received requests from 11 other counties, asking for a similar exhibit.

Case Finding.—Haenszel and Lade [245] state that, while the prevalence of all stages of syphilis is a measure of effectiveness of control measures applied to the preceding generation, incidence measures the success of present programs. Serologic surveys may yield information concerning prevalence in proportion to the adequacy of coverage of the population concerned, but little information concerning the incidence of new cases can be thus secured. Although case reporting yields information in reference to incidence which cannot be secured by survey methods, it is subject to the following defects: (1) incomplete coverage, because of infected persons who do not seek medical attention; (2) variation in discovery rates produced by fluctuations in the number and type of physicians serving the population; (3) duplication in counting cases resulting from the use of false names on case reports. Case report statistics, therefore, should be supplemented by methods which estimate the degree to which cases are reported as they occur. Such an estimate was derived from a comparison of case reports collected in upstate New York from 1936 to 1943 with Selective Service serologic reports. For the purposes of this paper it suffices to say that all laboratories performing serologic tests for syphilis are required to transmit to the health officer of jurisdiction a copy of each report in which the reaction is not negative. Case reports are secured, specific as to stage of disease by name of patient for 97 per cent of persons thus known to have a positive serologic reaction. The results were as follows: Of men 18 through 34 years of age found to have positive serologic reactions in the course of the Selective Service examinations, 40.6 per cent had been reported as cases of syphilis in upstate New York between 1936 and 1943. Of selectees with seropositive syphilis 13.67

244. Freeble, C. R.; Wright, E. O., and Bogue, R. S.: Mass Public Venereal Disease Education—Ohio Fairs, J. Ven. Dis. Inform. **30**:196-198 (July) 1949.

245. Haenszel, W. H., and Lade, J. H.: The Frequency of Discovery of Syphilis in Upstate New York Between 1936 and 1943, Am. J. Syph., Gonor. & Ven. Dis. **33**:579-586 (Nov.) 1949.

per cent under 25 years of age had been reported during the first year of their infection. In Buffalo and Rochester the percentage of cases reported prior to Selective Service examination was well in excess of the rate in the rest of the upstate area with respect to early syphilis, as well as to the later stages.

Syphilis Control Program in Iowa.—Heeren, Iskrant and Hibbets,[246] in evaluating the syphilis control program in Iowa since 1936, find that from 1936 to 1947 the mortality rate from syphilis dropped from 10.5 to 6.5 per 100,000 persons. For the same period the infant mortality rate was reduced from 0.4 to 0.02 per 1,000 live births. From 1936 to 1946, on the basis of rate of admission of syphilitic psychotics to psychiatric institutions, the incidence decreased from 4.1 to 2.5 per 100,000 population. From the morbidity reports of clinics and institutions the incidence of acquired syphilis has decreased in the past two years. On the bases of premarital and antepartum serologic testing there has been no decline in the prevalence of syphilis over the past seven years. Therefore, the reservoir of syphilis persists in Iowa.

Alabama's Blood Testing Program.—With the passage of a law in 1943 which required all persons between the ages of 14 and 50 to have their blood examined for syphilis, Alabama became a pioneer in the mass blood-testing field. It should be noted that there are four dovetailed parts to mass blood testing: education and blood letting; serologic testing; follow-up of positive reactors, doubtful reactors and those with unsatisfactory reactions, and treatment. Smith and Gill [247] report the results of Alabama's mass blood-testing program. They tested 79.82 per cent of the estimated 14 to 50 year old population. There were 1,450,513 persons tested for syphilis, and 94,636, or 6.5 per cent, diagnosed as having or having had the disease. White men had the lowest rate, 1.17 per cent; white women came next with 1.32 per cent. The rate for Negro men was 15.14 per cent, and the highest rate was in the Negro women, 18.78 per cent. An original survey and resurvey were carried on in nine counties. In the first survey 112,094 persons were tested, with 6,111 found infected. In the resurvey, 106,093 persons were tested and 2,954 infections were found. In the first survey 154 cases of primary and secondary syphilis were found, a rate of 1.4 per 1,000. The resurvey showed 242 instances of primary and secondary syphilis, a rate of 2.3 per 1,000. There is strong evidence that a 50 per cent reduction in syphilis prevalence was due to the discovery and successful treatment of infections at the time of the first survey. These workers also found an 80 per cent reduction in incidence of late syphilis.

Case Finding: Congenital Syphilis.—Statistical reports indicate that despite modern therapeutic methods the incidence of congenital syphilis has remained constant for the past 5½ years, although there has been a continuous decrease in infant mortality due to syphilis in the past 11 years, which in itself would indicate a decline in the incidence. Bowdoin and Jolly [248] believe that the incidence of congenital syphilis in Georgia will show a decided decrease within the next few years, as a result of a special program instituted to detect cases of congenital syphilis. In

246. Heeren, R. H.; Iskrant, A. P., and Hibbets, R. S.: The Control of Syphilis in Iowa, J. Ven. Dis. Inform. **33**:79-87 (March) 1950.

247. Smith, W. H. Y., and Gill, D. G.: The Effectiveness of Alabama's Mass Blood Testing Program, South. M. J. **43**:185-190 (March) 1950.

248. Bowdoin, C. D., and Jolly, J. J.: The Control of Congenital Syphilis: Prevention and Case Findings, J. Ven. Dis. Inform. **31**:50-52 (Feb.) 1950.

1948, 10 cases of congenital syphilis were discovered in a six month period. In a corresponding period in 1949, with the aid of additional investigators whose efforts were directed to detecting congenital syphilis, 38 times more cases were reported. Measures and methods employed in this campaign include (1) intensive case finding; (2) serologic testing of every school child in Negro schools (since 93 per cent of congenital syphilis occurred in the Negro); (3) family investigation of any child treated for syphilis; (4) investigation of all children of mothers treated for syphilis; (5) periodic serologic testing in patients attending antepartum clinics. In addition, legislative measures are being sought to permit recording of serologic tests and reactions on birth certificates to encourage follow-up studies by the private physicians.

Case Holding: Early Syphilis.—Suitable follow-up of persons treated for early syphilis is of the utmost importance, especially in view of the fact that many more relapses or reinfections occur following modern short intensive schedules of therapy than formerly were observed with prolonged courses of metal chemotherapy. That there are practical difficulties involved in obtaining patient cooperation in this matter is stressed by O'Malley.[249] In a series of 365 patients treated over a period of 7½ to eight days with penicillin plus arsenicals and bismuth, this investigator writes that, despite an active case-holding program, less than 50 per cent of the group reported at the end of three months, less than 40 per cent at the end of six months and less than 25 per cent at the end of one year. Only 76 (20.8 per cent) of the original group reported for examination of the spinal fluid during the sixth post-treatment month.

Case Holding in Patients Treated with Penicillin on an Ambulatory Basis.—Sorenson and Shannon[250] present experience with case-holding effectiveness among 200 patients treated on an ambulatory basis with daily administration of a slowly absorbed penicillin preparation (600,000 units of procaine penicillin in oil with 2 per cent aluminum monostearate) from September 1948 to February 1949 at the Denver General Hospital outpatient department. Treatment was completed in a high percentage of patients. The total treatment time up to 20 days, sex and previous treatment do not appear to be important factors in case-holding efficiency. On the other hand, although older patients and patients with later stages of disease have better records, the educational status of the patient is more apt to be responsible for good case holding. Therefore, this points to the importance of good patient education, especially in those who have recently acquired the disease. It was felt that treatment facilities should be such that they may be fitted to the patient's daily routine.

Two hundred and seventy-three patients were treated by Hayman[251] for early and late syphilis on an outpatient basis, on six, seven, eight and 10 day schedules. All received 600,000 units of penicillin daily. Eighty-six per cent completed treatment; 10 per cent missed one day, 3 per cent missed two days, and 1 per cent missed three days of treatment. Attendance for the six, seven and eight day sched-

249. O'Malley, C. K.: Penicillin in Early Syphilis: Results Obtained in 365 Cases, South African M. J. **24**:127-132 (Feb.) 1950.

250. Sorenson, R. M., and Shannon, R. D.: Case Holding in Out-Patient Therapy of Syphilis, J. Ven. Dis. Inform. **30**:281-285 (Oct.) 1949.

251. Hayman, C. R.: Rapid Treatment of Syphilis: A Second Study of Clinic Attendance, J. Ven. Dis. Inform. **30**:285-287 (Oct.) 1949.

ules was significantly better than that of the 10 day schedule. Treatment had to be discontinued in two cases owing to untoward reactions.

Venereal Disease Control Program of the United States Navy.—Dougherty [252] is of the opinion that, apart from the problems of disease control, venereal disease is associated with the exercise of individual judgment, conditioned by social, educational, cultural, religious, moral and previous sexual experiences. Promiscuity and venereal disease may be interpreted to evidence a degree of mental, emotional and social immaturity so far as the personal understanding and responsibility of sexual activity may be concerned. Generally, the Navy attempts to eliminate the worst and foster the best in the environment to which men are exposed. It also attempts to forewarn and strengthen the judgment of men initially and throughout their period of service. However, avoidance of exposure always rests with the individual person. The Navy is desirous of cooperating to its full extent and of protecting the family of the future from within. The latter may be accomplished by continually stressing the responsibilities of sexual conduct and the implications of promiscuity and educating the individual regarding his responsibilities of home, family and community.

Control of Syphilis in Seamen.—The importance of seaports in the epidemiology of venereal diseases has long been recognized. The international agreement signed in Brussels in 1924 was the first positive achievement in limiting this phase of the venereal disease control problem. Krzyanowski [253] has summarized the developments in this field since World War II, with particular reference to the postwar enlargement of Poland's coastal border. Free clinic facilities have been enlarged, informational pamphlets have been prepared and an effort has been made to keep physicians informed regarding recent advances in syphilology. In the Polish Port Dispensaries venereal infections constitute 40 per cent of all disabilities among seamen. That the problem continues to be acute is indicated by the fact that during comparable five month periods in 1948 and 1949 the number of patients treated increased from 283 to 291.

Control in Foreign Countries.—The coordination of venereal disease control in the Rhine area, advocated by the International Union Against Venereal Diseases and recommended by the World Health Organization Expert Committee on Venereal Diseases,[254] is a new aspect of international cooperation in venereal disease control. These organizations recommended that the facilities accorded Rhine River boatmen should be extended and developed by the following measures: (*a*) establishment of diagnostic and treatment centers in the principal river ports which do not as yet possess them; (*b*) free medical examinations, treatment and hospitalization not only for nationals of the country concerned but also for foreigners; not only for seamen and boatmen but also for their families living on the boats; (*c*) development or creation of social services, preferably specialized, so that epidemiological action can be taken and social assistance given to patients; (*d*) international tracing of infectious contacts through the exchange of epidemiological information;

252. Dougherty, W. J.: Venereal Disease Control in the Health and Moral Welfare Program of the United States Navy, J. Social Hyg. **35**:418-424 (Dec.) 1949.

253. Krzyanowski, M.: Control of Venereal Diseases in Seamen, Bull. Inst. Marine & Trop. Med. **2**:255-266, 1949.

254. Venereal Disease Control Among Rhine River Boatmen, Chron. World Health Organ. **3**:117-120 (June) 1949.

(*e*) distribution to patients, free of charge, of an individual treatment card issued by the World Health Organization in four languages (German, English, French and Dutch); (*f*) distribution to seamen of a folder giving a list of diagnostic and treatment centers.

Role of the Private Practitioner in Venereal Disease Control.—Turner [255] reports that in 1948 Santa Clara County, Calif., in cooperation with the United States Public Health Service and the Santa Clara Medical Society, sponsored a venereal disease educational project to demonstrate (1) that the private practitioner with support of the local health agencies can perform the essentials of venereal disease control, including case finding, diagnosis, treatment, contact interviews and post-treatment observation; (2) that a public education program, featuring symptoms and treatment and emphasizing the private physician as a public servant, can accelerate case finding for the physician and local health departments. To arouse the interest of the private practitioner, a series of articles on the various aspects of venereal disease appeared in the *Monthly Physicians' Bulletin*, published by the Santa Clara Health Department. In addition, the County Medical Society sponsored a meeting devoted to modern syphilotherapy. Public health nurses received a series of lectures on venereal disease control integrated into the total health program. The program for education of the general public employed a variety of mediums, including radio, newspapers, signs, movies, comic books, film strips, lectures and pamphlets. These materials stressed signs and symptoms of venereal disease and ease of cure and directed suspects to their physicians or health departments. As a result, the number of private physicians reporting cases, the number of cases of syphilis reported by private practitioners and the contacts reported by private practitioners, all showed a definite increase as compared with the reports of the previous year. The project demonstrated that the private practitioner, working together with the health department, can accomplish a venereal disease control program which will reduce the incidence of new cases.

Progress in Venereal Disease Control.—In a long presentation Stokes [256] comments on the therapeutic progress made in combating venereal disease since the introduction of the various antibiotics. He contends that the responsibility of the physician extends beyond mere treatment of these infections. To control and stamp out venereal disease the physician should also be concerned with human idealism, preservation of the family life, and education in the responsibilities of the member of the community to his fellows.

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255. Turner, W. E.: The Health Department and Private Physician Team in Venereal Disease Control, J. Ven. Dis. Inform. **31**:14-16 (Jan.) 1950.

256. Stokes, J. H.: The Practitioner and the Antibiotic Age of Venereal Disease Control, J. Ven. Dis. Inform. **31**:1-14 (Jan.) 1950.

News and Comment

NOTICES

Teaching Seminar in Proctology.—The International Academy of Proctology will present its first teaching seminar on proctologic subjects, including the more recent developments, in the form of a symposium and round table discussion in New York city, April 7.

Registration for the seminar will be limited in number and open to licensed physicians who are members of the American Medical Association, state or county medical associations and graduates of an approved medical school. Admission to the seminar will be by card only. Preference in registration will be given to those affiliated with the International Academy of Proctology.

Applications for registration or requests for further information should be addressed to Dr. William Lieberman, Chairman, Seminar Committee, International Academy of Proctology, 1819 Broadway, New York 23.

GENERAL NEWS

Laboratory Training Courses.—Courses to be given during 1951 at the United States Public Health Service Communicable Disease Center, Chamblee, Ga., will include Laboratory Diagnosis of Syphilis (February 12 to 23 and March 12 to 23); Microbiology for Public Health Nurses (February 26 to March 2); Laboratory Diagnosis of Bacterial Diseases, General Bacteriology, Part 1 (February 26 to March 9) and Part 2 (March 12 to 23); Laboratory Diagnosis of Parasitic Diseases, Part 1, Intestinal Parasites (March 5 to 23) and Part 2, Blood Parasites (March 26 to April 13), and Laboratory Diagnosis of Enteric Diseases, Part 1, Introductory Enteric Bacteriology (March 26 to 30). Information concerning the courses to be given during the remainder of the year and application forms may be secured from the Officer in Charge, Laboratory Training Services, Communicable Disease Center, United States Public Health Service, Post Office Box 185, Chamblee, Ga.

National Gastroenterological Association Award Contest for 1951.—The National Gastroenterological Association has announced its annual cash prize award contest for 1951. One hundred dollars and a Certificate of Merit will be given for the best unpublished contribution on gastroenterology or allied subjects. Certificates will also be awarded other physicians whose contributions are deemed worthy.

Contestants residing in the United States must be members of the American Medical Association. Residents of foreign countries must be members of a similar organization in their own country. The award will be made at the Annual Convention Banquet of the National Gastroenterological Association in September.

The Association reserves the exclusive right of publishing the winning contribution, and those receiving Certificates of Merit, in its official publication, *The Review of Gastroenterology*.

All entries should be limited to 5,000 words, typewritten in English, prepared in manuscript form and submitted in five copies accompanied with an entry letter. They must be received not later than June 1, 1951. Entries should be addressed to the National Gastroenterological Association, 1819 Broadway, New York 23.

Book Reviews

The Tuberculous Process: A Conception and a Therapy; A Private Study. By Alfred Leitch, M.B. Price, $3. Pp. 175. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1950.

This small book summarizes the opinions and experiences of a clinician who has had considerable experience with tuberculosis. There is nothing especially new presented, but readers may find the clinical experiences of Dr. Leitch of interest.

Transactions of the Eighth Conference on Liver Injury, New York, 1949. Edited by F. W. Hoffbauer, M.D. Price, $1.60. Pp. 164, with illustrations. Josiah Macy, Jr., Foundation, 565 Park Avenue, New York 21, 1950.

In this publication, the most recent of a series devoted to discussion of liver disease by prominent investigators in the field, the participants have maintained the high standard of presentation coupled with informality so characteristic of the earlier conferences. There are seven sections, each with free discussion. Recent studies of the anatomy of the liver lobule as revealed by quartz rod visualization and the function of the hepatic artery make up the first two. Then follow studies of massive liver necrosis, the role of liver and kidney in circulatory homeostasis and investigations of the metabolism of the eviscerate rat. The last two sections cover the problems of liver glycogen and hepatic cell protection and the locus of early dietary cirrhosis.

The Transactions should interest all investigators in the field of liver and metabolic disease as well as gastroenterologists and internists in general.

Textbook of Gynecology. By Arthur Hale Curtis and John William Huffman. Price, $10. Pp. 799, with 466 illustrations, 37 in color. W. B. Saunders Company, W. Washington Sq., Philadelphia, 1950.

The sixth edition of this widely used textbook now lists Dr. Huffman as co-author. Some of the sections have been rewritten; others have been revised. However, there have been no extensive changes in general format or manner of presentation.

As in other editions, this book is well and interestingly written. It is profusely illustrated, and practically all the drawings and photographs are of superb quality. New diagrammatic drawings in the section on embryology of the generative organs are particularly well planned and executed. They clarify an otherwise confusing subject.

As with most medical textbooks, each edition of this book has become longer and heavier. Also, as with most textbooks, the authors have ignored the general importance of certain subjects and have devoted inordinate amounts of space to those in which they are particularly interested. For example, the detailed and highly technical section on anatomy covers 79 pages.

This book will, no doubt, continue to be the standard textbook on gynecology. As a student textbook it is too long and too detailed, yet not sufficiently detailed to be considered a reference book. Operations are discussed and illustrated but not sufficiently well that the book could suffice as a textbook on operative gynecology. In the opinion of the reviewer the book suffers from trying to be all things to all people.

Steroid Hormones and Tumors. By Alexander Lipschutz, M.D. Price, $6. Pp. 309, with 111 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1950.

According to the author, this book is intended to be of use both to the research student and to the clinician. It will, no doubt, be of interest and of value to the research student but not to the clinician, unless he has specialized knowledge and interest in this particular field.

The book is limited almost exclusively to discussion of animal experimental work on the relation of steroid hormones and tumors. The bulk of it has to do with the production of

fibromatous growth by estrogens in the guinea pig and the prevention of this effect by simultaneous administration of other types of steroid hormones. Dr. Lipschutz and his co-workers have done and have published a tremendous amount of work on this subject in past years. These tumors are not autonomous, by the way. With cessation of estrogen stimulation, they spontaneously disappear. Many pathologists on this basis would object to calling them true tumors.

The semantically objectionable word "fibroid" is used in referring to these tumors. This term is used clinically for a uterine myoma, which the guinea pig tumor distinctly is not. In the first place, it has no particular predilection for the uterus but develops in the subperitoneal connective tissue anywhere in the abdominal cavity and, even, in the pleural cavity. Secondly, the uterine "fibroid" is basically a tumor of smooth muscle cells. The animal "fibroid" is basically a tumor of connective tissue origin.

The author also briefly but adequately reviews the animal experimental work on the relation of steroid hormones to the production of other types of tumors and points out the tremendous species differences in this regard. By inference at least he points out the inapplicability of most, if not all, of this animal data to the human being. He makes much of "antitumoral autodefense and steroid homeostasis." This reviewer had some difficulty in following him in these sections.

There are 111 illustrations. Most of these contain one or more photomicrographs of uniformly excellent quality. The cross indexing is adequate, and the bibliography is relatively enormous and seemingly complete. The author shows a refreshing honesty in one instance by specifying that he had read an abstract of the article and not the original.

The Ethical Basis of Medical Practice. By Willard L. Sperry. Price, $2.50. Pp. 185, with no illustrations. Paul B. Hoeber, Inc. (Medical Book Department of Harper & Brothers), 49 E. 33d St., New York 16, 1950.

The book is a result of requests received by Dr. Sperry, Dean of the Harvard Divinity School, following the delivery of several addresses on medical ethics, to expand and publish the material in book form. The book is small, and, for the most part, it is interesting and easy reading. The reader will find one ethical problem, euthanasia, and perhaps others, discussed in sufficient detail to be of real help. The author has the background to enable him to add color to his writing and the experience in the medical, as well as in the religious, field to promote better understanding and teamwork between the two professions. For example, he brings out clearly many of the difficulties facing the clergy in their attempts to administer to the sick, attempts which, because of their limitations, often appear of little value.

But if the reader is left with some feeling of disappointment, of incompletion, his feelings are probably justified. Dean Sperry's reputation alone is enough to promise the reader more than this book offers. The work is too short and the subject too profound to justify the rambling type of writing the author uses in a large part of the book. He touches on many minor as well as major subjects, and too often even those he discusses at any length are not hit squarely enough to benefit the reader greatly. The subjects include such topics as the relation of specialization to medical ethics, the differences between the humanist and the scientist, the specialist in contrast to the general practitioner, socialized medicine, the tragic moral choices forced on mankind and totalitarian medicine, especially in relation to the Nuremberg medical trials.

Not only his subject matter but also the level and direction of his writing are varied. He moves from a light, surface treatment of one subject to deep theological involvement in another, addresses sections to medical students as well as to physicians and ministers. This in itself is hardly undesirable, but when squeezed into a book this size it becomes an overambitious attempt which ends up saying too little about too much.

It is, however, this very shortcoming which may well be the book's greatest virtue. The author's inclusion of so many subjects, though not discussed as fully as might have been hoped, does open for the interested reader a wide field of thought. This regards particularly the medical student. For him, surely, great benefit is derived from having these questions raised for his own thinking before he is actually required to act on them.

Pathology of Articular and Spinal Diseases. By Douglas H. Collins, O.B.E., M.D. Price, $7. Pp. 332, with 199 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1950.

This is a record of the author's 15 years' experience and interest in the pathological aspects of articular diseases. The careful observations of articular and other related pathological changes, as well as clinical information pertaining thereto, are ably written and are supplemented by abundant illustrations of both gross and microscopic tissues. Perhaps a subsequent edition will present at least some of these in color. The text is easily read and especially free of typographic errors, an additional indication of the careful preparation of this book.

Included is a review, excellently prepared, of articular anatomy and embryology which will be of especial value to physicians not in daily contact, surgically or pathologically, with the tissues affected in rheumatic diseases. Other subjects discussed are trauma ("in no form of joint disease can the influence of trauma be entirely disregarded"), osteoarthritis ("the initial lesion is destruction rather than degeneration"), gout (including certain American concepts), rheumatic fever ("the case for an etiologic relationship between rheumatic fever and rheumatoid arthritis is not strong enough to be conclusive"), rheumatoid arthritis (the synovial pathologic changes are "virtually diagnostic"), bacterial arthritis, tumors and "disorders of the joints in diseases primarily affecting the other systems." The final five chapters discuss applied anatomy and diseases of the spinal column and disks.

The clinical experience of many rheumatologists will support the author's contention that spinal osteoarthritis is to be differentiated from spinal osteophytosis and that "no clinical syndrome is known to be associated with spinal osteophytosis" even though "the x-ray picture is often impressive."

The author finds it difficult to correlate his pathological experience, the reported results of use of cortisone and pituitary adrenocorticotropic hormone (ACTH) in rheumatic diseases and Selye's concept of "the alarm reaction" and his reported production in rats of "inflammatory arthritis" by overdosage of desoxycorticosterone acetate.

Rheumatologists, pathologists and orthopedists, as well as other physicians to whom rheumatic patients present themselves, will have frequent need for the informative and stimulating material in this commendable book. In the opinion of the reviewer, this book is one of the best, if not the best, available text on articular pathology.

Study of Structure in Relation to Function: The Esophagus and Pharynx in Action. First edition. By William Lerche, M.D. Price $5.50. Pp. 229, with 105 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1950.

This book consists of a consideration of the esophagus based on a study of 90 cadaver specimens from the dissecting room and 10 fresh esophagi. From his anatomic investigation the author has been able to define gastroesophageal and pharyngoesophageal segments of the esophagus and their action in regurgitation and deglutition. Of particular interest are the author's conclusions regarding the constrictor cardia and the superior and inferior esophageal sphincters.

The book is well illustrated with clearcut photographs of anatomic material and drawings from roentgenograms. It is a fundamental contribution on the esophagus, the result of much detailed, careful study, and contains a comprehensive review of the literature.

The Modern Treatment of Asthma: With Special Reference to Gold Therapy. By Laszlo Banszky, M.D., (Berlin), L.M.S.S.A. (Lond.). Price, $2.50. Pp. 135, with no illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1950.

The author of this book considers it established that tuberculosis is the commonest cause of bronchial asthma, an idea which is not accepted by the majority of internists today. He considers that the state of sensitivity established in this fashion may be reversed by the use of gold salts in the treatment of bronchial asthma. In his hands the results have been dramatic; 55 per cent of 203 patients of all ages suffering from asthma have been completely relieved two years or more after at least one course of nine weekly injections of gold sodium thiomaleate (myochrysine®). It is entirely possible that gold is capable of relieving an occasional asthmatic

person but certainly not through its antiphthisic properties. Whatever value it may have is probably mediated through the pituitary-adrenal cortex axis. In spite of the value of dimercaprol (BAL) in the control of gold toxicity, gold therapy is still a dangerous procedure. At present it appears far preferable to use pituitary adrenocorticotropic hormone (ACTH) or cortisone directly.

Tissue Culture Technic. By Gladys Cameron, with contributions by Robert Chambers and C. G. Grand. Price, $4.20. Pp. 191, with illustrations. Academic Press, Inc., 125 E. 23d St., New York 10, 1950.

This second edition should be of considerable value to those contemplating the use of tissue culture methods in research and teaching. The book is concise, lucid and well illustrated. The author has included many of her experiences which should prove to be of value to other workers. Although the number of pages is not large, the method is thoroughly presented.

Peptic Ulcer. By A. C. Ivy, Ph.D., M.D., D.Sc., LL.D., M. I. Grossman, Ph.D., M.D., and William H. Bachrach, Ph.D., M.D. Price, $14. Pp. 1,144, with 137 illustrations and 210 tables. The Blakiston Company (Division of Doubleday & Company, Inc.), 1012 Walnut St., Philadelphia 5, 1950.

To quote the authors, "This book is an ambitious attempt to present systematically all the worthy information and thought which bears upon the problem of peptic ulcer." We will leave it to the reader's judgment to decide how well they have succeeded. The foreword is by Drs. Sara Jordan, D. C. Balfour and A. J. Carlson. The work involved in the production of this volume obviously has been stupendous. For example, by actual count not only has reference been made to 3,316 noteworthy contributions to the literature, but each one has been critically reviewed, appraised and interpreted by the application of modern scientific methods, so that order has been brought out of a welter of conflicting opinions and conclusions of both an experimental and a clinical nature. Another by-product of such effort is the numerous tables, which, usually in chronological fashion, epitomize the results of investigators throughout the world of a given problem or subject, thus encompassing an unusual amount of information, in a small space.

The contents, apart from the preface and foreword, consist of four parts. Part I is an introduction to the problem of peptic ulcer, comprising six topics, among which may be mentioned definition, physiology, resistance of the stomach to digestion and healing of acute and chronic ulcers. Part II is on the pathogenesis of the peptic ulcer. Parts III and IV are respectively concerned with diagnosis and treatment. Since all three authors are physiologists, it is not surprising that more than 70 per cent of the book's contents deals with the subject matter comprised in the first two parts. Part II alone consists of 585 pages and contains 557 references to the literature! This is as it should be, because physiology is a fundamental phase of the problem with which the authors can deal authoritatively, thanks to a background supplied by their own numerous significant contributions, especially those of experimental nature by the senior author. Moreover, circumspect perusal of the briefer parts III and IV reveals the authors' intimacy with current problems of purely clinical nature, the solution of which should be expedited by their illuminating observations. Their conclusions with respect to choice and method of treatment, based as they are on impartiality and demonstrable fact in the light of present knowledge, may readily be taken to heart by physicians and surgeons alike.

It is unnecessary for this reviewer to recapitulate some of the many interesting highlights of the book, much as he is tempted to do so, because each of the 21 chapters therein is concluded with a summary, while each part has a summary chapter. This gives the reader ready access to the gist of the book's contents. The work should have its greatest appeal for the present and future investigator if for no other reason than that the authors throughout the volume point out the experimental and clinical investigations that need to be repeated and the new ones which should be undertaken in the solution of existing problems, and even suggest the design or method of procedure by which the latter should be carried out. The book will naturally appeal to the medical and surgical specialist in diseases of the upper part of the digestive tract even though he is familiar with much of the nature of the contents, if not with the methods of arrival at conclusions or opinions which he might well emulate. However, this reviewer agrees with Prof. Carlson that the book is also a "must" for our colleagues in general practice, physiology and neuropsychiatry.

Pneumoconiosis. By Arthur J. Vorwald, M.D. Price, $7.50. Pp. 671, with 192 illustrations. Paul B. Hoeber, Inc. (Medical Book Department of Harper & Brothers), 49 E. 33d St., New York 16, 1950.

Since 1941, when two women with an obscure pulmonary disease first came under observation at the Essex Sanatorium in Massachusetts, knowledge of and interest in the problem of beryllium poison have come a long way. The results of investigation and a summary of current knowledge are embodied in this handsome book. Finely printed and profusely illustrated, 39 articles by various experts deal with every conceivable aspect of this fascinating problem. There is a complete bibliography of approximately 700 titles.

Physician's Handbook. Sixth edition. Edited by John Warkentin and J. D. Lange. Price, $2.50. Pp. 380, with illustrations. University Medical Publishers, Box 761, Palo Alto, Calif., 1950.

The familiar and popular "Physician's Handbook," now in its sixth edition, is presented with a new format and a completely new set of author-editors. The contents have been arranged in a handier and more logical sequence, and the black-tabbed rapid index makes the various chapters more easily accessible. Additional sections on the theory and use of the electrocardiogram and the radioisotopes are included, and information on the newer antibiotics has been added to the sections on therapy. Hormone therapy has been brought up to date, with the inclusion of uses and dosages of pituitary adrenocorticotropic hormone (ACTH) and cortisone. Retaining its emphasis on quick reference to hospital procedures, factual data and clinical aids, this improved edition of the "Physician's Handbook" will be now more than ever an invaluable aid to medical students, interns and resident physicians.

Clinical Electrocardiography. By Francis F. Rosenbaum. Edited by Henry A. Christian. Price, $4.50. Pp. 200, with 82 illustrations. Oxford University Press, 114 5th Ave., New York 11, 1950.

In a period when authors of texts on electrocardiography apparently have vied with each other in their emphasis on novelty and technical advances within the field, this monograph may seem restrained to the point of dulness. One whose contact with electrocardiography was interrupted two decades ago would feel quite at home as he read the earlier sections of the book pertaining to disorders of the heart beat. Only as he reached the discussion of the form of the electrocardiogram would he realize that empiricism had given way to logic. But even here the technical advances represented in the central terminal method and the exploration of multiple precordial points are described only to an extent demanded in order that clarity may prevail in subsequent discussion of aberrations in form of the ventricular complexes.

This restraint is but a mark of maturity in attitude toward the subject of electrocardiography. Dr. Rosenbaum was reared on "the new gospel"; hence he has seen no reason either to justify it or to shout about it. He has reserved his energies for the more important job of presenting simply and concisely the fundamental concepts pertaining to formation of the ventricular complex and the alterations in that complex which attend injury and disturbances in intraventricular conduction.

This is a splendid text on electrocardiography. Only the test of use will determine whether the novice in the field will find its degree of condensation more than his powers can handle. A few more diagrams might prove helpful to one so afflicted, but perhaps they would make for dogmatism on points of theory as yet controversial.

The Causes of Blindness in England and Wales. By Arnold Sorsby. Medical Research Council Memorandum No. 24. Price, 1s. 6d. Pp. 42. His Majesty's Stationery Office, York House, Kingsway, London, W.C. 2, 1950.

From a thorough and scholarly analysis of a group of 19,149 certificates from a total of some 76,000 blind persons registered in England and Wales, various statistical studies of age, sex and cause are presented. These cannot fail to interest the reader with an academic interest in the cause and prevention of blindness. The progress of medicine in the almost complete eradication of such diseases as smallpox and ophthalmia neonatorum is reflected in the current statistics as compared with previous studies, some of which are briefly given.

Ninety-one per cent of the blind persons studied were blind in both eyes from the same cause, and it is somewhat surprising to learn that 24.6 per cent of cases were due to cataract, over one third of which were considered to be remediable. Glaucoma accounted for 13.4 per cent, myopia 10.8 per cent, congenital defects 9.9 per cent, syphilis 6.7 per cent, senile macular degeneration 6.4 per cent and ophthalmia neonatorum only 2.6 per cent. As was to be expected, industrial accidents were commoner in men, but diabetes was a much commoner cause in women than in men. The author estimates the rate of blindness in England and Wales as 200 per 100,000 population.

The author is to be commended for this study and for the impetus given to the important work being undertaken in various quarters in the prevention of blindness.

Pathology in General Surgery. By Paul W. Schafer, M.D. Price, $17.50. Pp. 580, with 495 illustrations, 368 in color. University of Chicago Press, 58th St. and Ellis Ave., Chicago 37, 1950.

Readers of medical literature are accustomed to seeing colored illustrations used frequently, and a few such figures are found in most textbooks, but in this really outstanding work 368 plates vividly portray the color of the tissues as they are seen in the gross or on the stained microscopic slide. An excellent addition in many instances is the inclusion of roentgenograms characteristic of the lesion. The illustrations could often be well used to explain to a patient his disease condition and what treatment is planned. Dr. Schafer has done a magnificent job in using color to stimulate our ever present interest in pathology, and a note of appreciation is also in order to G. D. Searle & Co. for their aid in furnishing the necessary engravings.

The format of the book is good, and the contents are arranged in a simple fashion, beginning with parietes and general aspects and passing to the vascular system, some endocrine glands, breast, lung and mediastinum, head and neck, esophagus, stomach, duodenum and small intestine, appendix, colon and rectum, pancreas, liver, gallbladder and bile ducts and peritoneum. The coverage for general surgery is so excellent that one can well wish the pathological aspects of gynecologic conditions, diseases of bones and joints and disorders in other specialties were equally embraced.

Conveniently, the description of a disease begins on the page facing the corresponding plates, and, most importantly, it is written from a viewpoint closely correlating the clinical aspects with the pathological. This will always be attractive to the busy practitioner, and the book is equally valuable to the internist and the surgeon. The fundamentals of treatment are briefly given and are uniformly sound. Each subject ends with a few references for those wanting more extensive information.

The student preparing for examinations in which microscopic slides are used should find the colored illustrations, rather than those in black and white, particularly valuable for review purposes. As an illustrated synopsis of important disease conditions the book is a splendid reference for nurses, dietitians, medical technicians and others in ancillary fields.

This publication is really a superb accomplishment. The colored plates are so attractive that the volume comes quickly to mind when thinking of pathology in general surgery. Those who thumb through it will wish to read it thoroughly, and it should be in the library of every general surgeon.

Lehrbuch der Röntgendiagnostik. Lieferung II: Skelett. By H. R. Schinz, W. E. Baensch, E. Friedl and E. Uehlinger. Price, 70 German marks. Pp. 878, with 1,271 illustrations. Georg Thieme, Diemershaldenstrasse 47, (14a) Stuttgart O; Agents for U. S. A.: Grune & Stratton, Inc., 381 4th Ave., New York 16, 1950.

In view of the high distinction of the authors of this book and of the series of six volumes to which it belongs, it is not surprising that this fifth and revised edition has been called for. The disorders and conditions of bone are classified in six major categories, namely, aseptic necrosis in epiphyses, apophyses and small bones; toxic osteopathies; inflammatory diseases of bone; primary medullary osteopathies; congenital abnormalities with bone changes, and primary tumors of bone. Individual subjects are discussed with typical German thoroughness; illustrations are abundant and excellent, and the typography is of superior quality.

It is the impression of this reviewer that the text is more readily translatable than usual and that even those of us whose German is rusty or limited can read the book with fair understanding. Roentgenologists of mature age who can recall the scantiness of roentgenologic literature three or four decades ago will note the sharp contrast with the encyclopedic magnitude of the complete six volume series on diagnosis.

Medizinische Mikrobiologie: Parasiten, Bakterien, Immunität. By Reiner Müller. Price, 26 German marks. Pp. 542. Urban & Schwarzenberg, Thierschstrasse 11, München 2; Meinekestrasse 13, Berlin W. 15, Germany, 1950.

In this book the author has divided the subject matter into four main categories: (1) parasites, (2) bacteria, (3) fungi and (4) immunity.

In any volume of this size which sets out to cover the subject of medical microbiology, one will always be able to find errors. These are few and occur usually when the author attempts to stress the therapy of the various disease processes under discussion. There is great emphasis on the historical background of each of the various topics covered, which unquestionably makes for a clearer understanding of the matter at hand. For example, in the discussion of cholera, the author alludes to Tchaikovsky's continued drinking of raw water from the Neva River, although he was warned, and his subsequent death from the disease. At another point he discusses the possibility that the Leptospira of Weil's disease, which was quite common in the eighteenth and nineteenth centuries, might have been the etiologic agent for the disease of many of the 70,000 persons who died of so-called yellow fever during the War Between the States. Dr. Müller is unquestionably on sound ground here. Weil's disease is clinically indistinguishable from yellow fever, and A. M. Stimson (A Note on an Organism Found in Yellow-Fever Tissue, *Pub. Health Rep.* **2**:541, 1907) reported that an organism morphologically similar to the spirochete of Weil's disease was seen in the kidney tissue of a patient who died of so-called yellow fever in the New Orleans epidemic of 1905.

To anyone who reads this book it must be readily apparent that the author has spent many fruitful years in the field and has excellent knowledge of the subject. One is a little surprised at the frequent Latin and Greek quotations, which the author implies are readily understandable by the "classically" educated physician. The reviewer can unreservedly recommend this book to any physician who has a reading knowledge of German; it is an extraordinarily delightful and detailed treatise.

Manson's Tropical Diseases. Thirteenth edition. By Sir Philip H. Manson-Bahr. Price, $9. Pp. 1,150, with 412 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1950.

This book continues to be one of the most outstanding in the world on the subject of tropical disease. It is a complete single volume concerned with tropical medicine, but, like all single volumes, it is not truly encyclopedic. This thirteenth edition has been brought up to date to include the new antibiotic drugs and the experiences obtained during World War II. This book is highly recommended to students of tropical medicine, especially those interested in the British points of view.

Principles of General Psychopathology: An Interpretation of the Theoretical Foundations of Psychopathological Concepts. By Siegfried Fischer, M.D. Price, $4.75. Pp. 327. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1950.

As one might suspect from the subtitle of this book, it is not altogether easy reading. The reviewer must admit that there are sentences and even paragraphs which he cannot understand at all. This is, however, no criticism of the book, since the language of psychopathology seems obscure to many readers who have not made a special study of the subject, and even psychiatrists themselves differ in their views.

Consciousness, memory, thought, emotion, etc., are at best difficult subjects, and even though all is not made entirely clear this is a readable and interesting book.

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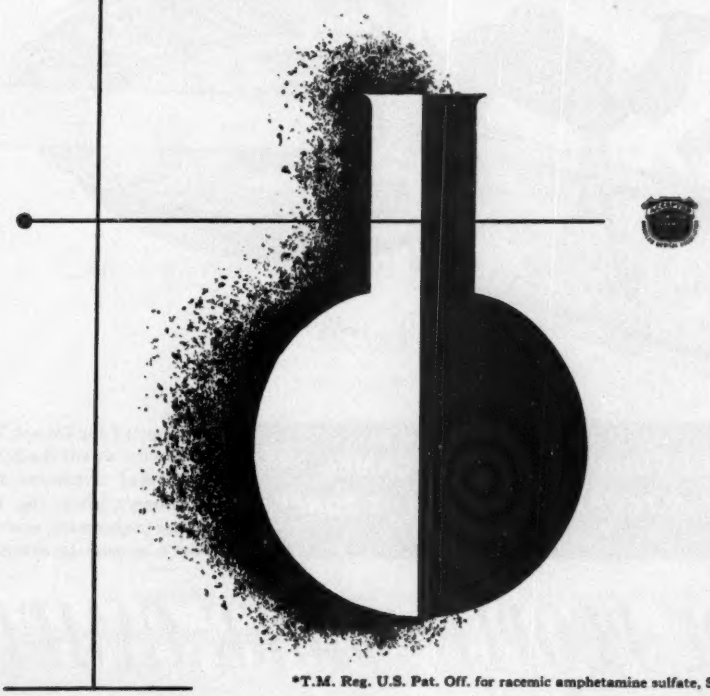

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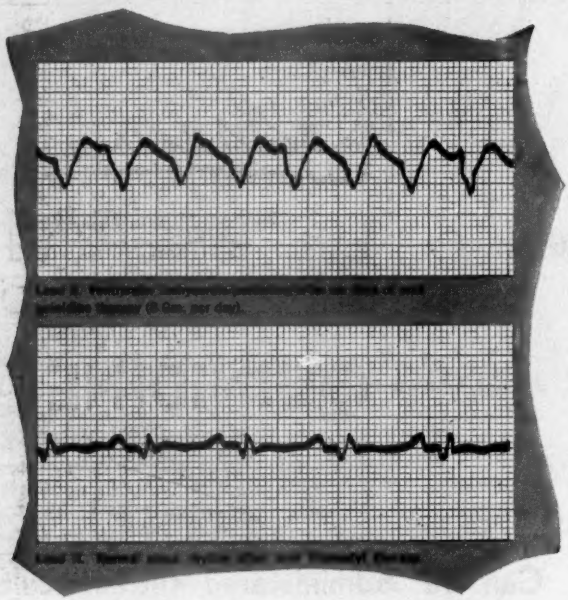

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1. Internat. Abstr. Surg. *83*:1, July 1946.
2. Am. J. Obst. & Gynec. *49*:114, Jan. 1945.
3. J.A.M.A. *128*:1152, Aug. 18, 1945.